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ORIGINAL ARTICLES.

I. A CLASSIFICATION OF THE DISEASES OF LIPOID METABOLISM AND GAUCHER'S DISEASE.*

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The concept of xanthomatosis includes a series of clinical and anatomic conditions in which lipoid substances are deposited in certain tissue systems or organs of the body, thus producing a yellow discoloration of these tissues or organs. There exist, however, certain doubts concerning the desirability of this designation. First of all, the expression is misleading insofar as the word xanthoma contains the ending "oma" and leads one to think of a neoplasm, which is true only for certain isolated cases of xanthomatosis. Second, the term suggests the erroneous idea that the deposited lipoids are all of a certain type. On the contrary, in the various forms of xanthomatosis the lipoids occur in quite different forms and, therefore, by no means always produce the same yellow discoloration of the affected zones. As there is no uniformity in the nature of these deposits, the term is wrongly used to designate the entire group of these diseases. Also in the diffuse skin xanthomatosis of diabetes the color is produced by the so-called lipochromes contained in neutral fat and not related to lipoids. However, as it would be difficult to eradicate this firmly established word and to replace the term "xanthomatosis" by the much more suitable

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term "lipoidosis," in the further analysis and classification of the xanthomatoses, we must attempt to make up by strict precision for the lack of accuracy in the general term.

Classification of Xanthomatoses. We first divide the xanthomatoses into two groups, namely, generalized and localized. The generalized forms consist of: (1) the symptomatic or secondary forms, those which accompany other diseases and are symptomatic manifestations of disturbances of lipoid metabolism associated with these diseases; (2) the essential or primary forms, those which constitute disease entities in themselves and are based upon a constitutional anomaly of lipoid metabolism.

The following are examples of the symptomatic xanthomatoses: Multiple or generalized xanthomata (or xanthelasmas) in diabetes or in liver diseases which are associated with jaundice and in chronic kidney disease. They occur as pea or bean-sized yellow or brown deposits or nodules in the skin. They are generally flat; the larger ones may sometimes be tuberous and are often surrounded by a hyperemic zone. They are found especially on the extensor surfaces of the extremities, notably about the elbows and the knees.

In these lesions the lipoid is deposited mainly in proliferating cells of the connective tissue of skin and in the endothelium of lymph vessels. The tremendously enlarged cells contain closely packed droplets and needles which consist of a cholesterin fatty acid ester. They stain with Sudan and are doubly refractile. When the lipoids are extracted by alcohol in the microscopic section large foam cells can be observed. In diabetes, as well as in cases of jaundice, the substances which are deposited in the xanthoma cells (cholesterin fatty acid ester) appear in the blood stream in an increased and often considerable quantity. In 1906 I, therefore, explained the symptomatic xanthomatosis in these diseases on the basis of a cholesteremia and a selective absorption of the cholesterin fatty acid ester by the xanthomatous cells. In this way it is easy to understand the recurrent eruptions and the transitory character of these lesions. In some cases the cells of the internal organs also take part in this cholesterin fatty acid ester storage, thus giving rise to a form of a visceral xanthomatosis. In 1 of my cases, for instance, after jaundice of long duration due to liver cirrhosis, a pachymeningitis interna xanthomatosa was found. Sometimes when a diabetic patient with lipemia dies in coma the spleen may be affected in a characteristic manner, in addition to the lipoid deposits which may be present in the skin, the lymphatic and hematopoietic systems, the suprarenal cortex, the intima of the aorta and the endocardium. The spleen in such cases may be twice the normal size and weigh 450 gm. The pulp may be completely infiltrated with large clear cells which, according to the variable character of the lipemia, probably represent a mixture of neutral fats, phosphatids and cholesterin fatty acid esters. The

inclusions, according to their chemical character, give the well-known microchemical reactions for fat and lipoid substances in varying degrees. In the microscopic section of such a spleen, the large phagocytes appear as distinct foam cells. It is noteworthy that they spring entirely from the reticulum cells of the pulp. The endothelial cells of the splenic sinuses are entirely unaffected even when they are situated in the midst of large accumulations of foam cells.

The variability in the character of the intracellular lipoids in such a spleen forms a definite contrast to the uniformity of the cholesterin-fatty acid esters in the diabetic xanthomatoses of the skin or inner organs. However, the difference in the distribution of the deposition of lipoids easily explains this. The faster the lipemia develops, the greater is the variability and the less is the purity of the accumulated substances.

Conversely, in the usual subchronic form of diabetic xanthelasma, the picture in the spleen is less prominent and the character of the deposited substance is more pure and uniform. We then find cholesterin fatty acid esters.

We next consider the essential or primary xanthomatoses. Only the researches of the last decade have cleared away much confusion and a number of precise pathologic entities have emerged which can be well differentiated clinically and anatomically.

In this group belong: (1) Gaucher's disease, (2) Niemann-Pick's disease, (3) Hand-Schüller-Christian's disease, (4) the primary non-symptomatic external and internal xanthomatoses which occur in varying distributions and intensity in the skin and in the inner organs.

We are able to differentiate these diseases not only by their clinical and anatomic properties, but also according to the chemical character of the deposited lipoids. To a certain extent we can use for this purpose the microchemical properties of the lipoid cell contents in addition to their morphologic and optical appearance. Cholesterin fatty acid esters are sudanophilic and doubly refractile. Phosphatids are blackened intensely by the Lorrain Smith-Deitrich method but they are optically inactive, while the lipoid in Gaucher's disease cannot be stained at all and is not doubly refractile. Of course, it is recognized that the value of all microchemical tests is a very relative one. The lipoids in these cases are not in pure form but always in mixtures. Their staining properties are influenced by other substances in the cytoplasm and the specificity of the histochemical methods for differentiation of all fats depends upon the character of the mixture of fats or lipoids. We have, therefore, augmented the histochemical methods by exact chemical analyses of the affected organs. It was especially the Viennese pathologist, Epstein, who successfully showed that the deposited lipoids in the group of primary xanthomatoses are of various chemical natures.

It must be recognized, however, that his methods and results have not been wholly accepted.

A further step forward has been made by the observation that in certain disease groups, for instance, in Gaucher's disease and in the essential internal xanthomatoses which do not yet have a special name, the skeleton is affected to a prominent degree. There really are subgroups consisting of osseous forms with special chemical and roentgenologic pictures. In Hand-Schüller-Christian's disease the bone lesion is a regular and leading symptom.

Further attention has been paid to the relation between the primary xanthomatoses and the reticuloendothelial system of Aschoff, with its single cell forms as, for example, endothelial cells, reticulum cells, histiocytes, etc. Gaucher's disease has even been characterized as a disease of the whole reticuloendothelial system (Aschoff) while Niemann-Pick's disease has been designated a lipoid histiocytosis (Bloom). You will see later that these designations are either too inclusive or do not designate the extent of the lesions.

Finally, investigation of the various types of the primary xanthomatoses has brought experimental lipoid cell hyperplasia into prominence. These so-called exogenous cholesteroses have been produced experimentally by Chalatow, Anitschkow and Verse and their coworkers, by feeding lipoid to animals.

The outstanding forms of essential xanthomatoses, namely, Gaucher's, Niemann-Pick's, Hand-Schüller-Christian's disease and the less regular forms, will form the main topic of my lectures.

The last group in the classification is composed of the localized xanthomatoses, that is, xanthomatous deposits in only one area of the body. They may be non-neoplastic in character. Of this group the xanthomata in the skin of the eyelids are the best-known form. They consist of circumscribed yellow spots or nodules. The localized xanthomatoses may be true neoplasms, xanthomatous blastomata, sarcomata or, less frequently, carcinomata. In each case accumulation of lipoids in the tumor cells produces the xanthomatous appearance. Recurrences of these tumors, however, are not at all different from ordinary carcinomata or sarcomata. Other authors and I have seen, for instance, metastasizing foam cell carcinomata of the prostate. A special circumscribed type of purely local neoplastic xanthomata is the *xanthoma en tumeurs* of the skin, found generally on the knee, the elbow or the heel. They consist of firm tumors up to the size of a hen's egg. Their cut surfaces are dull white or yellow, containing some gray or brown spots. These tumors originate in the subcutaneous tissue. They are cellular sarcoma-like tumors and the foam cells are packed with doubly refractile substances. The tumors otherwise contain many multinucleated giant cells and iron pigment. They recur locally but rarely are there distant metastases.

For all these local forms of xanthomatosis cholesterinemia has been postulated as a *conditio sine qua non*. Systematic examination will be necessary before we know whether this is a fact or whether nonspecific localized disturbances in the lipoid metabolism of the tumor cells underlie this form of xanthomatosis.

Gaucher's Disease. We now turn to Gaucher's disease. This disease was described in 1882 by Gaucher as a primary epithelioma of the spleen; the disease is thus just 50 years old. In 1900 Bovaird, of New York, claimed that Gaucher's disease is non-neoplastic and is an endothelial hyperplasia in the spleen, liver and lymph nodes. In 1907 Schlagenhaufer designated the disease as a systematic affection of the reticulum cells of all the lymphatic and hematopoietic organs, including the bone marrow. In the same year, 1907, Marchand recognized the importance of a deposit of foreign substance in the histogenesis of the Gaucher cells. Mandelbaum and Downey, in 1916, founded the modern conception of the disease as a metabolic disturbance, and in 1924 Lieb and Epstein, by chemical analysis of the spleen, demonstrated the lipoid nature of the Gaucher substance. They show that kerasin is its more important constituent. Kerasin belongs to the cerebrosids (sphingogalactids). These facts give you a short history of the disease.

Gaucher's disease is not very rare. Since I started my investigations the number of cases reported in the international literature has rapidly increased to more than 75. It is congenital and familial in occurrence, since in about one-third of the cases several members of one generation are concerned, but the disease is limited to this generation only. About twice as many cases occur in females as in males. The enlarged spleen and liver may be noticed as early as the first months of life. The disease may lead to death in infancy. The symptoms are those of rapidly progressing cachexia, though the main symptoms may be cerebral with spastic paralysis and psychic disturbances. Generally, however, the large spleen is discovered accidentally in childhood. The enlargement of the liver usually occurs after the spleen has reached considerable size.

Furthermore the splenic and liver tumors show a progressive increase in size, although relatively the liver grows less rapidly than the spleen. The course is frequently quite chronic and in some cases extends over many decades. The oldest patient on whom I did a postmortem examination was 56 years. The organism, in this extraordinary duration of the process, adjusts itself to the organ changes. Even with the gigantic size of the spleen and liver the symptomatic disturbances are often strikingly slight. The superficial lymph nodes do not usually take part in the changes and are, therefore, as a rule, not palpable. Involvement of the bones in the usual case is noted by pains in the lower ends of the femur and tibia or by tenderness over the sternum and ribs.

As early signs are to be noted the characteristic pigmentation of

the skin and definite blood changes. The diffuse or spotty pigmentation, mostly confined to the face, neck and hands, shows a yellow brown to ochre tone. In addition there occur brownish-yellow wedge-shaped thickenings of the scleræ, the base of the wedge lying toward the margin of the cornea. All of these pigmentations are expressions of a general hemochromatosis which is constantly present in this disease and becomes more marked with increased duration of its course.

The blood changes consist first of a leukopenia which may be due to a diminution in polymorphonuclears or lymphocytes. Then there follows a moderate hypochromic anemia. At no time are there Gaucher cells present in the blood stream. Often one sees a thrombocytopenia early in the disease, related perhaps to the hemorrhagic diathesis which characterizes the late stages of the disease. Most often there is bleeding from the nose or gums and sometimes hematemesis, melena, uterine bleeding and hemorrhage in the connective tissue, muscle and skin, occasioned by slight trauma, may occur. Death is only rarely the sequel of cachexia or rapidly progressive anemia; more usually it is due to intercurrent diseases, such as pneumonia, sepsis, tuberculosis, carcinoma, etc., and in infants to bronchopneumonia. Patients may die following splenectomy.

In a clinical differential diagnosis one must consider splenic anemia, Banti's disease, familial splenomegaly, acholuric icterus (hemolytic icterus) and Hanot's biliary cirrhosis. There is no pathognomonic clinical symptom but we possess a simple and excellent diagnostic aid, namely the microscopic examination of material from a puncture of the spleen or of bone marrow obtained from the tibia or sternum. The material obtained on puncture always shows in fresh or stained smears the large characteristic Gaucher cells. Occasionally one can demonstrate even in the minutest particles obtained on puncture the specific tissue structure of the Gaucher spleen.

Gross Pathologic Anatomy. The picture is frequently dominated by the extreme enlargement of the *spleen* which may weigh as much as 8100 gm. In 24 cases in adults I found an average splenic weight of 2700 gm. (compared to about 250 gm. normally); in 7 cases in children between the ages of 5 and 14 years, the average weight being 1800 gm. The organ is very firm and tough and shows on cut section a very characteristic appearance. The reddish-gray, pink or sometimes chocolate-brown background is always thickly stippled with innumerable gray-white or gray-yellow markings which close in to form a fine anastomosing network. They correspond to accumulations of Gaucher cells.

A second common characteristic of the Gaucher spleen is formed by larger or smaller nodular cavernous foci which are always multiple, and which occur only rarely in the normal spleen. Its dark

red surface on section shows thick blood-filled dimples or meshes. As a result of organization, they are transformed into globular, solid, calloused, fibrous nodules. Other irregular fibrotic foci correspond to a scarlike substitution of masses of Gaucher cells and still other foci represent scarred anemic or hemorrhagic infarcts.

A *liver* weight of 3300 gm. in 7 cases in adults (in comparison with 1500 to 2000 gm. normally) shows marked enlargement but the increase in weight of the liver is relatively less than that of the spleen. Interspersed in the brownish-red, yellowish or chocolate-brown parenchyma of the liver there can be seen small pale spots or conglomerated areas not unlike leukemic infiltration (Fig. 1). At other times there is a cirrhosis-like picture, without the usual changes found in cirrhosis.

Much less significant are the changes in the *lymph nodes* and in the *bone marrow*. The superficial lymph nodes, as I have already said, remain normal in size; the intraäbdominal and intrathoracic glands, although almost always involved, hardly ever reach the size of a walnut (2 cm. in diameter) and are at the same time colored more or less brown by heavy deposits of pigment. Grossly the bone marrow is either entirely unchanged, or, like the spleen and liver, shows whitish, spotted deposits.

As signs of *hemachromatosis*, which belongs to the anatomic and clinical picture of Gaucher's disease, I have already mentioned the yellowish-brown discolorations of the skin and sclera, and the occasional chocolate-brown color of the parenchyma of the spleen, liver and lymph nodes. The wall of the uterus and the mucous membrane of the uterus, stomach and intestines also may be involved. In all these cases of pigmentation one must always determine whether the pigment has merely originated from a local hemorrhage which may occur as an expression of a widespread hemorrhagic diathesis.

Pathologic Histology. The study of the Gaucher cells concerns, first of all, the *spleen*. The whitish spots correspond to foci of Gaucher cells, mostly sharply confined in alveolar fashion (Fig. 2) which are more or less thickly interspersed in the parenchyma of the spleen. Only rarely are they spread diffusely. In fresh specimens the Gaucher cells are homogeneous, opaque, dull-hyalin in appearance. With the Mallory stain, with acid-fuchsin, anilin-blue-orange G, and with previous fixation with picric acid and ammonium bichromate, they appear a light blue, and under higher magnification show, in their cytoplasm, an irregular network, bound like spider webs with the finest thread-like fibrils. Through these the cytoplasm appears wrinkled rather than foamy or roundly vacuolated. The wrinkles correspond to the remains of the spongioplasm in whose meshes the Gaucher substance is stored. Large cells with this type of cytoplasm are found in no other affection. The cells measure from 20 to 80 μ in their largest diameter; they

are polymorphous and often furnished with projections. The nuclei are either single or multiple and not infrequently are quite numerous. I have counted as many as 21 in a single cell. They are most often pyknotic. In those cells where there is a single nucleus, it is often eccentric in position, generally near the cell border. Mitoses are disputed (Figs. 3 and 4).

An important finding which I have regularly observed in my examinations that seems to have completely escaped previous observers consists of arterial branches within the nests of Gaucher cells. They lie in part centrally, in part eccentrically. They occur most often singly but they may be double or appear as a main stem with branches (Fig. 5). The intima and media are always intact as are usually the innermost cells of the adventitia.

The Malpighian bodies remain quite passive. They may be replaced by Gaucher cells.

Pigment is absent only in children and infants, otherwise it is present without exception and increases in quantity with increased duration of the disease. It is, as the Turnbull reaction shows, mostly hemosiderin. Aside from the cells of the splenic trabeculæ, it is present in the endothelial cells of the venous sinuses and in the Gaucher cells themselves.

There is a second noteworthy finding which I was able to demonstrate in the spleen. In all the cases of Gaucher's disease which I examined I found the endothelial cells of the venous sinuses containing hemosiderin, without exception, but no Gaucher substance. The Gaucher cells contained in many cases no hemosiderin at all; at other times there was either slight or more marked diffuse hemosiderosis. In every instance, however, they were far poorer in their hemosiderin content. Erythrophagia on the part of the Gaucher cells may occur, but is not the rule.

Bone marrow giant cells, megakaryocytes, which occur in the Gaucher cell alveoli as well as in the pulp of the Gaucher spleen, indicate foci of blood formation. Near them one finds the usual elements of hematopoiesis.

The blood spaces of the cavernomata are lined by a simple endothelium containing large amounts of hemosiderin. This is regularly interrupted by groups of Gaucher cells from the periphery or from the septa. Except for the Gaucher cells, these spaces frequently contain all the elements of myelopoiesis (Fig. 6) in addition to intracellular or extracellular blood pigment. Nearby there are miniature cavernomata, that is, groups of cavernous vascular dilatations of microscopic size. In some Gaucher spleens these are the only kind of cavernoma and occur in very large numbers.

Of special histologic interest, finally, is the disappearance of the Gaucher cell parenchyma which, as I have already said results in calloused, fibrotic nodules. The Gaucher cells are not destroyed by fatty degeneration, caseation or a special type of degeneration.

Rather, the simple necrotic or atrophic cells disappear by a gradual diminution in size and simultaneously there develops intercellularly a firm connective tissue, whose meshes develop into fibrotic nodules.

In the *livers* of infants and young children the Gaucher cells are found exclusively in the capillaries. In older children and in adults the Gaucher cells help produce a peculiar cirrhotic thickening of Glisson's capsule and disintegration of liver lobules (Fig. 7).

This process is distinguished from the usual liver cirrhosis by the following characteristics:

1. The cirrhotic connective tissue contains always small nests of Gaucher cells, generally in large numbers. The Gaucher cells have here a distinct tendency to stretch, to arrange themselves in bundles and form syncytia. Each cell lies in a reticular mesh.

2. In contradistinction to ordinary cirrhosis, there is no antecedent granulating proliferation which causes the production of connective tissue.

3. Bile duct proliferation is generally lacking.

As in the spleen, the pigmentation in the liver increases during the course of the disease. In later stages there is always hemosiderin in Glisson's capsule, but the Gaucher cells in the latter contain hardly any pigment.

In the *lymph nodes* the capsule and the trabecular system become markedly thickened and the lymphadenoid parenchyma is replaced by Gaucher cells which lie in individual meshes of fibrous tissue. There is, however, no characteristic relationship of the lesions to the degree or the duration of the disease. The amount of pigment —generally and predominantly hemosiderin—is usually higher than in spleen and liver.

The *bone marrow* shows a number of peculiarities, even in those cases of Gaucher's disease where it is not prominently involved.

1. There is, as in the lymphatic system, no direct relation between the intensity of the Gaucher cell deposits and the duration of the disease. The whole skeleton may be affected in a year-old infant.

2. There are marked variations in the amounts of Gaucher cells deposited in the individual bones, and in the particular form of storage. At times we find the Gaucher cells quite diffusely scattered; at other times in poorly delimited confluent foci, and then again only in small cellular nests or isolated collections.

3. Brill, Mandelbaum and Libman have already shown the peculiar tendency of Gaucher cells in bone marrow to stretch and change their configuration. These elongated and frequently spindle-shaped cells are distinctly wrinkled or finely fibrillar and striated. Delicate connective tissue and reticulum fibers course between the single cells, often intimately fused with the periphery of the cell. Here also the gradual disappearance of Gaucher cells due to atrophy and necrosis and the concomitant thickening of the intercellular fibrous network may cause the development of large calloused foci.

Finally, the pigmentation in the bone marrow, as in other organs, is irregular and insignificant.

The *pigment* of Gaucher's disease is predominantly hemosiderin as far as the hematopoietic and lymphatic system is concerned. Iron-free pigment, originating from protein, plays a lesser rôle, but is found occasionally in large amounts outside of the hematopoietic and lymphatic apparatus, in smooth muscles of the intestines, stomach, uterus or in voluntary musculature; furthermore, in the vascular wall and in connective tissue in these and other locations. Autogenous pigment also causes the brown discoloration of the skin, according to my investigations. All these iron-containing and iron-free pigments are expressions of the general hemachromatosis, *i. e.*, increased blood destruction.

Do Gaucher cells occur outside of the above-mentioned organs of the hematopoietic, lymphatic and vascular system? Do organs, other than the spleen, the liver, the lymph glands and bone marrow, contain Gaucher cells?

The answer to these questions is in the affirmative, if applied to cases of Gaucher's disease in infants. Histologic study has demonstrated the presence of unmistakable Gaucher cells in the thymus, tonsils and the lymphatic apparatus of the intestine, perhaps also in the lungs. But there is a very plausible explanation for these exceptions. Lubarsch's investigations on the phagocytosis of iron pigment and fat in infants have shown that the potency of phagocytosis of certain cell groups of infantile organs changes about at the end of the first year. By that time cells capable of storage up to that time (the reticulum cells of the thymus, the perivascular cells of the suprarenals, the lymphoreticular cells of the intestine or of the tonsils) lose their phagocytic capacity. Therefore, you may find Gaucher cells in infants, in places where they are missing in the adult.

Two findings represent the essential morphologic characteristics of Gaucher's disease:

1. The large cell infiltration limited to the spleen, liver, lymph glands and bone marrow.

2. The peculiar morphologic type of the Gaucher cell, particularly the character of the cytoplasm. Certainly the Gaucher cell is the proper morphologic representative of Gaucher's disease.

According to newer investigations in infants, it seems that the Gaucher substance may be stored in additional places, for instance, in the pyramidal cells of the cerebral cortex. Such changes have been first pointed out by Oberling and Woringer. They describe a "progressive cortical atrophy." Lindau, a Swedish author, has lately shown that the changes in the ganglion cells and their dendrites resemble morphologically those found in the familial amaurotic idiocy of Tay-Sachs. They provide a very plausible explanation for the psychic disturbances and the spastic paralysis

to which these infants succumb. The inclusion in the ganglion cells and their dendrites are microchemically inactive, as is the Gaucher substance itself. Whether this change is a regular occurrence in Gaucher's disease of infancy remains as yet unproved.

If, as we have seen, the Gaucher cell is the morphologic pathognomonic sign of Gaucher's disease, then there arises the question, What is *the substance that causes the peculiar appearance of the Gaucher cell?*

As I said previously, the Gaucher substance is optically and microchemically inactive. Mandelbaum's dictum that a microchemical finding of neutral fat, myelin-like or doubly refractile substance in suspicious cells excludes the presence of Gaucher's disease still holds true. The problem can only be solved by chemical analysis of the organs.

Lieb and Epstein succeeded in finding the solution of the problem. According to their results, the Gaucher substance is essentially kerasin which belongs to the cerebrosids. Such large amounts of it are stored in the Gaucher spleen that they may comprise up to 10 per cent of the dried spleen. Epstein finds in addition to kerasin only alcohol (not ether) soluble phosphatids in the mass of the Gaucher cell complex. Kerasin precipitates from solutions in diluted alcohol in the form of needle-shaped crystals, which aggregate in characteristic spherical and rosette-like configurations (Fig. 8).

As you have heard, autopsy on the newborn shows that at this time the Gaucher cells are found in the spleen, liver, lymph nodes and bone marrow. In addition, contrary to previous views, one sees that the process in the spleen, liver, lymph nodes and bone marrow is a diffuse one from the very onset, even though the spleen dominates the pathologic and clinical picture. The enlargement of the liver may not follow until later. From this it follows that it is only the rapidity of growth which is of interest in the further development of the disease.

Osseous Types. This "participation curve" of the organs in Gaucher's disease may be altered in an extraordinary way. There is a form that is clinically and anatomically preponderantly osseous. Here one must assume a special constitutional redisposition of the skeletal system, and this is supported by the observation that at times all the affected members of a Gaucher family in one generation may have the osseous form of the disease. In these cases two related constitutional deficiencies must be at play—the one, the predisposition to Gaucher's disease in general, the other a special localization in the skeletal system as a manifestation of a particular deficiency of the mesenchyma. I have seen this in 5 brothers, on 2 of whom I was able to carry out complete autopsies and histologic investigations of the skeletal system. These osseous cases where the process is so generalized in the skeletal system that scarcely a bone is spared give the disease a completely altered clinical aspect.

These may remain unrecognized during life and be regarded and treated as tuberculosis or syphilis of the bones. The localization in the skeletal system, as we learn from the postmortem examination, is not only absolute but also relative, that is, the weight of the spleen and liver, despite the predominant involvement of the bones, is less than the average weight of these organs in Gaucher's disease. In the small and flat bones, for example, in the calvarium, the markedly porous spongiosa is filled with a yellow or gray deposition, either diffusely or in a speckled form. This diffuse or speckled form is also the prototype of both forms which occur in the marrow cavity of the long bones. In the marrow cavity nodules of the size of a walnut lying close together partly encapsulated with fibrous tissue more or less pigmented, sometimes hemorrhagic or scarred, are conspicuous and reveal with the still remaining yellow or gray-red marrow rests, a strikingly variegated picture (Fig. 9). A diffuse tough mass may fill the marrow cavity like a plug, broken up partially by the still intact marrow substance (Fig. 10). It is sharply defined from the compact bone by a thick, pale, partially osseous boundary. The cortex appears coarsely vacuolated and may be very thin. The cortical vacuoles and cavities are filled with yellow and red tissue. The infiltrating Gaucher cell masses can cause swelling of the bones, for instance, in the lower femur and the upper third of the tibia. The much thinner compact bone naturally may be subjected to spontaneous fracture. Invasion of the head of the femur, with depression fracture and resulting deformity, leads to a deforming arthritis of the hip joint. This is the cause of irreparable limping. Especially severe changes result from the complete Gaucher infiltration of the vertebræ. They are reduced to one-half or even one-third of their normal size (Fig. 11). The body length is correspondingly shortened. In the lower dorsal or upper lumbar regions some of the vertebræ are crushed into a mortar-like mass. A gibbus results. The neighboring vertebræ or intervertebral disks show no special reaction. The crushed vertebra is converted into a yellowish-brown calcium containing fragment and disappears slowly due to the union of the other vertebræ, just as in certain cases of osteoporosis (Fig. 12). When the vertebra disappears the intervertebral disks unite. In all these changes of the osseous form the superficial areas and the periosteum remain intact and smooth. The cortical portions, no matter how thin, are never penetrated.

Even the microscopic pictures reveal striking peculiarities.

The elongation and spindle-shaped forms of the Gaucher cells, as found in the usual cases in the bone marrow, rise here to the highest potency. One finds spindle-shaped Gaucher cells in bundles which become interwoven in the greatest diversity (Fig. 13). In these situations the spindle cells are usually long and reveal sharp striations.

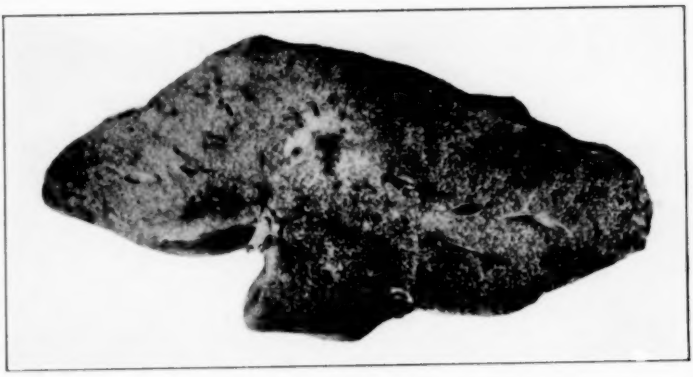

FIG. 1.

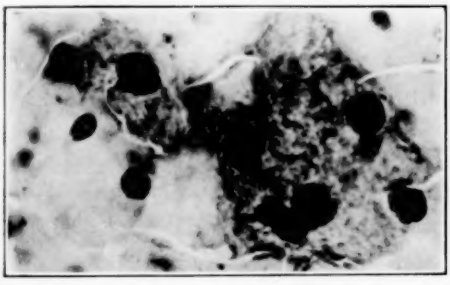

FIG. 3.

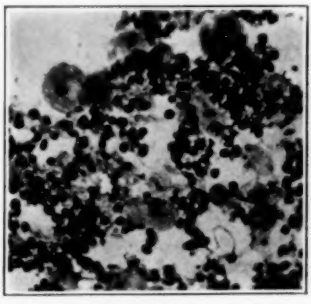

FIG. 4.

FIG. 1.—Liver in Gaucher's disease. Gray-white stippling in the parenchyma.

FIG. 2.—Section of Gaucher spleen. Nests of Gaucher cells.

FIG. 3.—Smear of material obtained on splenic puncture. Pappenheim stain. Multinucleated Gaucher cell. Cytoplasm wrinkled. There are no vacuoles.

FIG. 4.—Splenic tissue obtained by puncture in case of Gaucher's disease. Many Gaucher cells among pulp cells.

FIG. 5.—Nest of Gaucher cells with centrally located small artery.

FIG. 6.—Contents of one of the spaces of a cavernoma in a Gaucher spleen. Among the Gaucher cells are elements of myelopoiesis and several megakaryocytes.

FIG. 7.—"Cirrhosis" of the liver in Gaucher's disease.

FIG. 8.—The Gaucher substance. Kerasin crystals.

FIG. 9.—Dorsal half of left femur illustrating the skeletal form of Gaucher's disease. The marrow cavity is filled with nodules of Gaucher cells. Note atrophy of cortex and clublike swelling of the lower third.

FIG. 10.—Section through right tibia illustrating skeletal form of Gaucher's disease. The marrow cavity is diffusely filled with Gaucher cells. Rarefaction of the cortex.

FIG. 11.—Median section of the vertebral column of skeletal form of Gaucher's disease. Note destruction and collapse of 11th and 12th thoracic and 5th lumbar vertebræ. The intervertebral disks are not involved.

FIG. 12.—Median section of vertebral column in skeletal form of Gaucher's disease. Right half. Note destruction of 9th thoracic and 4th lumbar vertebræ. Gibbus. Intervertebral disks were not involved.

FIG. 13.—Microscopic section of Gaucher nodule from the marrow cavity of femur (see Fig. 9). Spindle-shaped Gaucher cells in bundles and interlacing in every direction. The fat cells in the bone marrow are preserved between them.

STATE OF IOWA

FIG. 2.

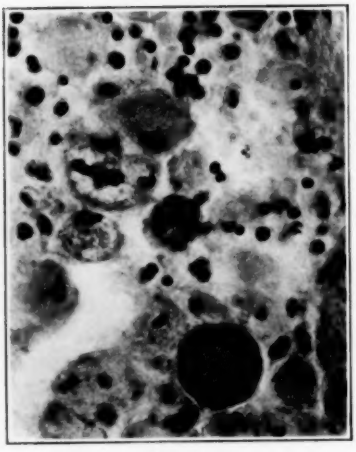

FIG. 6.

FIG. 8.

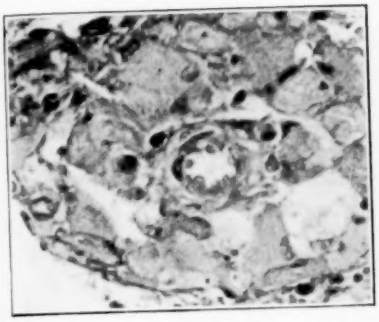

FIG. 5.

FIG. 7.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

FIG. 13.

If it is considered *a priori* that the spindle shape of the Gaucher cells in the bone marrow is a result of compression, this fascicular type of growth contradicts this view. It represents a particular type of growth in itself. Microscopic examination confirms the observation that the cortex of the bone is never infiltrated by Gaucher cells even where it is thinnest. I have never found a single Gaucher cell in the periosteum nor on the surface of the bone, even in those cases in which the marrow cavities were completely filled. When finally the cortex, as, for example, in the case of the vertebræ, becomes completely atrophied by the expansive pressure of the Gaucher cell masses, the situation is entirely different. In this instance the masses of Gaucher cells lie free, so to speak, and further proliferation causes a bulging of the dura mater and a compression of the spinal cord.

One succeeds in making a correct clinical diagnosis of the nature of the bony disease in the osseous form of Gaucher's disease when the ordinary stigmata of the condition, for instance, the enlargement of the spleen and liver, pigmentation of the skin, pinguecula-like lesions of the conjunctiva and the hemorrhagic diathesis, are most evident. Moreover, this affection of the bones possesses a number of characteristic Roentgen pictures whose peculiar appearance may lead to a correct diagnosis.

On the Roentgen film the bones appear less opaque because of the generalized atrophy and deficiency of calcium. They are coarse-grained and worm-eaten because of the extreme porosity. The cancellous bone may show large defects, together with marked thinning of the cortex. In the shafts of the long bones there appear at times the outlines of large nodules within the medullary cavity. Collapse and deformity of the head of the femur are visible in the Roentgen film. In children the center of ossification of the head of the femur disappears when the flattening takes place. In the diffuse, as well as the more circumscribed widening of the medullary cavities of the long bones, the clublike swelling of the lower part of the femur often becomes evident. Especially noteworthy in diffuse involvement of the shafts of the long bones is the picture of an apparently reduplicated cortex, and in the vertebræ, compression of the lower dorsal or upper lumbar vertebræ. The intervertebral disks appear unchanged, whereas in tuberculous caries of the spine they are soon destroyed. Moreover, there are no reactive or regenerative changes in the bone and periosteum which are characteristic of Pott's disease and other diseases of the spine. Not only in the spinal column but also elsewhere, the Roentgen film shows the complete integrity of periosteum and the cartilage, even in severely involved portions of the skeleton. This certainly constitutes an abundance of roentgenologic evidence.

In some of the cases the skeletal changes became prominent after the spleen had been extirpated. It is conceivable that the removal

of the spleen which constitutes the main reservoir of the Gaucher substance is responsible for the involvement of the bones in such an intensive and extensive form. This hypothesis, however, is not absolutely necessary, for in such cases the liver and the lymph nodes might equally substitute for the spleen. However, the value of splenectomy as a therapeutic measure remains a problem.

VALUE OF SPLENECTOMY. Here opinions differ. In a recent compilation a not inconsiderable number of cases, 19.5 per cent, did not survive the splenectomy. It is admitted that in a number of the cases there is an improvement in the general nutrition and the condition of the blood and a disappearance of the hemorrhagic diathesis. On the other hand, it may be emphasized that in other cases the disease process itself progresses and that the involvement of the skeletal system, as I have stated, becomes evident only after the splenectomy. Since the spleen, in the course of Gaucher's disease, represents solely or almost entirely an organ depot, its extirpation can, in my opinion, have no influence on the process. There is, therefore, no rational indication for its removal. The symptomatic indication is another matter. In cases of especially severe anemia, hemorrhagic diathesis or where there is a particularly large organ, splenectomy may be indicated. However, the prognosis of the operation becomes worse in just these cases of severe anemia and copious hemorrhages, because of the poor general condition of the patient. Radiotherapy of the spleen has also been tried. The splenic enlargement may be diminished by this means but there is no noticeable influence upon the course of the disease.

ORIGIN OF THE GAUCHER CELL. The questions now remaining for discussion are the histogenesis and the pathogenesis of Gaucher's disease. What is the origin of the Gaucher cell? Does it arise from the endothelial cell or the reticulum cell?

In the spleen, for example, which has been the most important object of histologic study, do the nests of Gaucher cells arise from a proliferation of the endothelium of the walls of the sinuses? Is their alveolar form due to the shape of the sinus? Or are they of reticulum cell origin? Or is Gaucher's disease to be reckoned offhand with the functional hyperplastic diseases of the reticuloendothelial system, as Aschoff maintains? Is the controversy over this or that form of separation of types superfluous, considering that there is essential fundamental identity of endothelial and reticulum cells? Actually, a not inconsiderable number of authors have without undue consideration identified the histogenetic behavior of the reticuloendothelial storage cells in experimental storage of dyes, cholesterol, protein mixtures, etc., with the histogenesis of the lipoid storing Gaucher cells.

There is, I believe, hardly a more striking example of the invalidity of the solution of morphologic problems by means of biologic functional induction. Especially in the case of the Gaucher spleen

there is morphologic proof, according to my observations, that the Gaucher cells arise from the reticulum cells—and only from these cells, and the endothelial cells remain completely uninvolved in the storage of Gaucher's substance. The very fact that in a considerable number of cases arterioles are found within a part of the Gaucher cell alveoli, shows that at least not all the Gaucher nests can arise from the endothelium of the venous sinuses. But the iron reaction of the splenic tissue makes it clear that the sinus endothelium is completely excluded as the maternal source of the Gaucher cells. If sections of the Gaucher spleen are treated with the Turnbull reagent, the pictures show most significantly that there is no Gaucher substance in the venous sinus endothelium, but, as a rule, only hemosiderin in considerable amounts; and conversely that the Gaucher cells which store the Gaucher substance contain either none or very irregularly distributed hemosiderin and purely in a facultative manner. This is an ever-recurring principle of the structure of the Gaucher spleen. On this account there occurs in Gaucher's disease an apparent and complete functional separation between endothelial and reticulum cells. Certainly in this instance, as in the diabetic xanthomatoses, the factor of time is of distinct significance. In animal storage experiments the organism becomes overloaded with relatively large amounts of storage substance in a short time, and because of this the entire storage system is activated. In Gaucher's disease the storage experiment of Nature extends over decades, and thus allows the especially differentiated tendency toward storage to proceed in its purest form. The reticulum cell origin of the Gaucher cell is also demonstrated in the lymph nodes and the bone marrow, while the endothelial origin remains unproven. However, by this observation alone, their origin is not settled. In the Gaucher cell nests of the spleen it can be shown with certainty that the Gaucher cells can arise from the adventitial and periadventitial cells, that is to say, the tissue histiocytes of the arterioles of the pulp. Thus in the liver the Gaucher cells arise from the connective tissue histiocytes of Glisson's capsule, the adventitia and periadventitia of the capsular vessels and the central veins. Therefore, Gaucher's disease is neither a "reticuloendothelial" disease, a disease of the entire "histiocytic apparatus" nor a histiocytomatosis, nor is it a pure reticulum cell disease. In addition to the reticulum cells of the spleen and the liver, the parent cell includes also the connective tissue cells of the bloodvessels of the adventitia and periadventitia and in addition the cells of Glisson's capsule. It is hence impossible to stigmatize Gaucher's disease with a mighty designation as a "reticuloendothelial disease."

Pathogenesis. Pathogenetically, Gaucher's disease exemplifies a primary congenital and familial metabolic disturbance on a constitutional basis. The metabolic disturbance is primary for all the

anatomic changes and clinical signs, just as the diabetic metabolic disturbance is for diabetic symptoms and visceral xanthomatoses, or the cholesterol feeding for cholesterin steatosis. The significance of the constitutional basis is indicated by the early onset, the familial occurrence, the predominance of the female sex and the susceptibility of the Jewish race. From several sources there has been assumed as the cause of the metabolic disturbance a primary disease hyperfunction of the reticuloendothelial system, because of the physiologic significance of the reticuloendothelial system as a metabolic apparatus. According to this viewpoint, it conditions at the same time the disturbance in metabolism and the storage of Gaucher substance. Proof for this viewpoint has not been presented. Every basis for it is lacking. One cannot even say whether the Gaucher substance is brought to the cells in finished form, or in the form of its building stones; whether "storage" corresponds to increased ingestion or diminished excretion, and whether the rich production of kerasin signifies an increase or merely a disturbance of normal metabolism. When one speaks of "storage" in Gaucher's disease, he does it only in a designative sense, because of the obscurity of all these factors.

For the clarification of hemachromatosis in Gaucher's disease, one considers that there exists in lipoid-storing cells of every sort the tendency to simultaneous storage of hemoglobinogenic pigments; also that with every added stimulation of the reticuloendothelial system there occurs an increased hemosiderosis, that is, an increased blood destruction. Therefore, in Gaucher's disease as well, the generalized lipoidosis is accompanied by an increased destruction of erythrocytes, that is, by hemochromatosis, for which, indeed, the persistent lipoidal overloading of the blood supplies a probable toxic cause. The facultative hemosiderosis of the Gaucher cells is only a special case of this general accompaniment of lipoidophagia.

The anemia of mild or severe intensity as well as the thrombopenia is based on the Gaucher cell infiltration of the bone marrow. The myelopoiesis in the Gaucher cell tissue, also in the cavernomas of the spleen, is compensatory; and, as I have already indicated, the thrombopenia is of significance for the hemorrhagic diathesis. Obviously these views on the pathogenesis of Gaucher's disease lie far within the realms of hypothesis.

A surer explanation of its developmental nature, I believe, can be offered on the basis of one fact, namely, the extraordinary constancy of the clinical, macroscopic, histologic, histogenetic, chemical and histiochemical findings which are present in Gaucher's disease and which are not repeated in any other comparable pathologic process. This is evident in the enormous chronicity of the process which from the beginning develops into a pure morphologic and chemical tissue reaction, quite in contrast to the experimental lipoidophagia or the lipoidophagia of the spleen in diabetic xantho-

matosis, or above all, the disease which I shall discuss in my second lecture, the lipoid splenohepatomegaly of the type of Niemann-Pick. The recognition of the latter disease as directly related to Gaucher's disease, but with, nevertheless, opposite essential disturbances of lipoid metabolism, has excluded many difficulties in the clinical-anatomical definition of Gaucher's disease and has enabled me to define this disease as sharply as I have attempted to do today.

SPONTANEOUS SUBARACHNOID HEMORRHAGE.

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In 1859, Samuel Wilks[1] wrote:

"Of all the difficult cases admitted into hospitals, those are the most perplexing where the patients are brought in in an insensible condition, and unable to give any account of themselves . . . and the surgeon has to choose between injury, poison, or disease, as a cause of his insensibility. . . . We refer in the present article especially to cases where an effusion of blood is found on the surface of the brain, without any apparent injury to the organ, and the question arises as to whether the cause be a blow, or arise from disease. . . . We therefore relate some cases where the effusion was spontaneous. . . ."

This introduction to Wilks' paper may serve equally well for a preface to the present one, in which is presented a series of 12 cases of spontaneous subarachnoid hemorrhage (hemorrhage into the subarachnoid space not caused by trauma) observed at the Baltimore City Hospitals in the last 3 years.

Previous Reports. Wilks[1] reported cases of spontaneous subarachnoid hemorrhage together with cases of traumatic origin. In 1912, Ehrenberg[2] reported 2 cases and reviewed 29 from the literature, for the first time describing spontaneous subarachnoid hemorrhage as a distinct clinical entity. Following that, the continental periodicals contained a number of case reports, but the malady was more or less overlooked in England and America. Leopold,[3] in 1924, deplored this fact and reported 3 cases of his own. The stimulus of Symonds[4] excellent paper, however, produced numerous case reports in the English-speaking journals, among which are those of Neal,[5] Packard and Zabriskie,[6] Richardson,[7] Hall,[8] and McIver and Wilson.[9]

Pathogenesis. Several conditions have been identified as causes of spontaneous subarachnoid hemorrhage and many others sus-

pected. The following list is offered in an attempt to classify the various etiologic factors:

I. Blood Dyscrasias.

II. Extrinsic Diseases Affecting the Bloodvessels of the Subarachnoid Space.

(1) Meningococcus meningitis.
(2) Tuberculous meningitis.
(3) Meningovascular syphilis.
(4) Embolism: (*a*) infected; (*b*) malignant.
(5) Heat stroke.

III. Intrinsic Abnormalities of the Bloodvessels.

(1) Thrombosis.
(2) Degeneration of the bloodvessel wall: (*a*) arteriosclerotic; (*b*) hypertensive; (*c*) in acute infections (as typhoid fever); (*d*) from poisoning (as alcohol)(?).
(3) Congenital nevi.
(4) Congenital aneurysms.

I. Cases of subarachnoid hemorrhage have occurred in various blood dyscrasias, as pernicious anemia,[10] sickle-cell anemia,[11] hemophilia and leukemia. The infrequency of reported cases is probably due to the fact that subarachnoid hemorrhage is often overlooked in the presence of the predominating disease. The present series contains no cases of this kind.

II. Pyogenic and tuberculous conditions in the meninges may cause necrosis of vessel walls with resulting hemorrhage, but actually this rarely occurs, because in tuberculous meningitis there is eccentric thickening of the adventitia and obliterative thickening of the intima—conditions which are not likely to result in rupture—while in meningococcic meningitis there is infiltration of polymorphonuclear leukocytes around the vessels, but little involvement of the vessel wall. There are no cases in the present series.

With respect to meningovascular syphilis, Turnbull[12] says that the usual lesion in smaller arteries is an obliterative endarteritis with thrombosis. In some cases, however, in which the adventitia and media become weakened before the intima has thickened, he states that rupture may occur.

Sands[13] recently reported 2 cases and stated that, while syphilitic meningitis as a cause of subarachnoid hemorrhage is rare, it does occur, and may be overlooked.

In 4 cases (3, 5, 7, 10) in the present series, there was a positive blood Wassermann reaction, and in Cases 3 and 7 positive reactions on the cerebrospinal fluid as well. Meningovascular syphilis may be considered as a likely etiologic factor in these instances. This proportion of cases associated with syphilis (33 per cent) is high as compared with Symonds'[14] report of less than 10 per cent, but the former figure is not surprising in a hospital in which 7.5 per cent of the patients have a positive Wassermann reaction.

Emboli of various kinds may initiate rupture and hemorrhage, but this is usually an insignificant part of the larger disease.

Cases of subarachnoid hemorrhage have been reported as due to heat stroke. McKenzie and LeCount[14] found minute hemorrhages in the leptomeninges in 2 out of 37 autopsies performed upon patients dying from heat stroke. In these cases the cerebrospinal fluid was clear and colorless, but it can be assumed that in some instances these hemorrhages might be sufficient to cause yellow coloration of the fluid. In Case 1, the patient became unconscious while working in the sun on a very hot morning. Heat stroke may have been the causative factor.

III. The largest class is that in which there is some abnormality of the vessel itself. Leadingham[15] reported a case of sinus thrombosis causing hemorrhage into the subarachnoid space.

In a number of instances there is present hypertension or arteriosclerosis, or both. In 5 cases (2, 7, 8, 9 and 11) in the present series of 12, the blood pressure was considerably above normal and remained elevated during convalescence. In Case 7, syphilis is a factor to be considered in addition to hypertension.

Subarachnoid hemorrhage associated with nevi has been reported by Cushing.[16]

Considerable data and not a few theories have accumulated upon the subject of aneurysm of the intracranial vessels. The articles by Fearnsides[17] reporting 44 cases, and by Wichern[18] reporting 21 cases, are the first comprehensive reviews.

Of the later papers, those by Parker[19] and Forbus[20] are distinct contributions. The former attempts to correlate autopsy and clinical findings, and shows that there is a difference in the clinical picture between rupture of the anterior arteries of the circle of Willis and their branches, and rupture of the posterior group.

Forbus found muscular defects in the media of cerebral arteries in cases of aneurysm and in some cases in which no aneurysms were found. These defects he traced to defective embryonic development. He believes that the repeated pounding of the blood column against these weak points will cause aneurysms, which eventually may rupture.

In the present series Case 5 was found at autopsy to have a ruptured aneurysm of the right anterior cerebral artery. Cases 4 and 12 may have been due to ruptured aneurysm, but the presumption is made by elimination, since the patients showed no evidences of syphilis, arteriosclerosis, hypertension or acute infectious disease.

Analysis of Symptoms. The onset was sudden in 7 cases, slow in 4, and in 1 instance was unknown. In the 11 in which the onset was known, it occurred with a sudden loss of consciousness in 6, once accompanied by delirium and once by delirium and convulsions. In the remaining 5, headache was the first symptom.

The various symptoms present in the 12 cases reported are listed

in Table 1, according to the frequency of their occurrence. Headache, while present as the initial symptom in 5 cases, was complained of at some time during the course of the illness by 9 patients. The syndrome began with unconsciousness in 6 cases and unconsciousness came on later in a 7th case. Three of the patients, after recovering consciousness, remained dull, sleepy and apathetic for a variable period, ranging from a few hours to 2 weeks in duration. Headache was accompanied by pain and stiffness of the neck in 3 cases. Vomiting and delirium were each present in 2 cases, and the other symptoms enumerated in Table 1 in 1 case each.

TABLE 1.—SYMPTOMS PRESENT IN 12 CASES OF SPONTANEOUS SUBARACHNOID HEMORRHAGE.

	No. of cases.	Percentage of total cases.
Headache	9	75
Unconsciousness	7	58
Dullness and sleepiness	3	25
Pain and stiffness of neck	3	25
Vomiting	2	17
Delirium	2	17
Paresthesias of scalp	1	8
Soreness along spine	1	8
Specks before eyes	1	8
Diplopia	1	8
Transient hemiparesis	1	8
Stiffness of legs	1	8

TABLE 2.—SIGNS PRESENT IN 12 CASES OF SPONTANEOUS SUBARACHNOID HEMORRHAGE.

	No. of cases.	Percentage of total cases.
Hyperactive deep reflexes	5	42
Choked disks	4	33
Unequal pupils	4	33
Hypoactive deep reflexes	3	25
Absent abdominal reflexes	3	25
Positive Kernig's sign	2	17
Positive Babinski's sign (or equivalent)	2	17
Nystagmus	2	17
Pulse-rate below 50 per minute	2	17
Seventh nerve paresis	2	17
Twelfth nerve paresis	1	8
Strabismus	1	8
Positive Brudzinski's sign	1	8
Absent deep reflexes	1	8
Leukocyte count above 10,000 per c.mm.	5	42
Temperature above 100° F.	5	42

Analysis of Signs. As shown in Table 2, the tendon reflexes were the most variable signs. Hyperreflexia was present in 5 cases, hyporeflexia in 3, and absence of deep reflexes in 1. Papilledema was found in 4 cases, unequal pupils in 4, nystagmus in 2 and strabismus in 1. Transient weakness of the facial nerve occurred in 2 patients, and of the hypoglossal in 1. Other abnormal signs were: absent abdominal reflexes, 3 cases; positive Babinski

sign or its equivalent, 2 cases, and positive Brudzinski sign, 1 case. All the abnormal signs cleared up during the patients' stay in the hospital, except in the 2 instances where death intervened.

Leukocytosis and moderate increase in temperature for the few days following the hemorrhage have been noted as occurring rather frequently. As will be seen in Table 2, each occurred in nearly half of the present series. The highest leukocyte count was 23,800 per c.mm. in Case 11.

Diagnosis. The usual clinical picture of subarachnoid hemorrhage is the sudden onset of unconsciousness, usually preceded by headache. Unconsciousness may last for a few minutes or several days and may be followed by dullness and drowsiness, by convulsions and delirium, or merely by a slight headache, which soon wears off and leaves the patient feeling perfectly well. The importance of headache as a suggestive symptom of hemorrhage into the meninges is well shown in Table 1, especially if accompanied by pain and stiffness in the neck.

Meningeal irritation or direct pressure effects are responsible for the signs. The deep reflexes may be hyperactive, normally active, diminished or absent. Superficial reflexes may be absent and various pathologic signs may be found, especially the Babinski sign. Papilledema, either unilateral or bilateral, and slowing of the pulse rate are the most suggestive signs of increased intracranial pressure.

Remembering that subarachnoid hemorrhage is more often overlooked than erroneously diagnosed, the important feature in the diagnosis is to suspect its presence and perform a spinal puncture in every case of coma, unless some other causative factor is certain. The present series of cases would suggest also that in instances of headache unexplainable on any other basis, consideration of subarachnoid hemorrhage and consequent spinal puncture are warranted.

If the spinal fluid contains blood there are only a few conditions to be ruled out. Traumatic blood introduced at the time of puncture is differentiated in three ways from bloody spinal fluid caused by hemorrhage into the subarachnoid space:

1. In the traumatic puncture the blood is not evenly mixed with the cerebrospinal fluid, but will color the first of 3 successive tubes darker than the third; in subarachnoid hemorrhage all the tubes will be colored alike.

2. The former will clot (if there is a sufficient amount of blood); the latter will not.

3. If the bloody fluid in subarachnoid hemorrhage be centrifugalized immediately, or allowed to stand, the supernatant fluid will be xanthochromic.

If the puncture is not done until several days after the onset the fluid may no longer be bloody, but merely xanthochromic.

In addition to subarachnoid hemorrhage, bloody or xanthochromic

fluid may occur in intraventricular hemorrhage, in cerebral hemorrhage with rupture into the ventricles or into the subarachnoid space, and in traumatic meningeal hemorrhage.

Patients with intraventricular hemorrhage show profound prostration and rarely recover. If they do not die they usually show residual paralyses. Hemorrhage into the substance of the cerebrum will show more lasting effects than subarachnoid hemorrhage, and often leave permanent paralyses.

Traumatic hemorrhage is often hard to differentiate, even at autopsy. Munck,[21] in analysis of 9 debatable cases, gives useful pointers for making the distinction. If there is fracture of any bone of the skull, if there are signs of trauma on the scalp, or if the hemorrhage is found at necropsy to be confined to a small area over which injury is known to have occurred, the case may be considered traumatic. In the absence of sufficient trauma, especially if there is demonstrable disease of the bloodvessels, the hemorrhage is classed as spontaneous.

Treatment. The relief of intracranial pressure is the end sought for; whether by repeated spinal drainages, intravenous hypertonic glucose solutions, or frequent doses of magnesium sulphate by mouth.

At the present time the accepted procedure at the Baltimore City Hospitals is to perform one puncture for diagnostic purposes and no more for 1 week (unless marked pressure symptoms require it). This time is allowed for the bleeding vessel to attain some degree of repair. After this the patient is given a puncture every 3 days (or oftener, in the presence of markedly increased intracranial pressure) until the fluid is colorless and the abnormal signs and symptoms have all disappeared. Intravenous glucose and drastic purgation are reserved for cases in which spinal drainage alone fails to give relief.

Case Reports. Case 1 (Med. No. 17516).—J. S., a colored male, aged 41 years, fell unconscious while at work on a hot summer morning. He roused from coma after 3 hours, but was alternately stuporous and raving on admission to the hospital.

The relevant findings on examination were: pulse, 120; moderate neck rigidity; irregular pupils with the right larger; slight sclerosis of retinal vessels; slight left facial weakness; normally active deep reflexes; moderate sclerosis of peripheral vessels; blood pressure, 110 systolic, 80 diastolic.

Urinalysis: albumin ++; many white cells (negative after 2d day). The leukocytes were 11,200 per c.mm. The spinal fluid was bloody and became xanthochromic on subsequent taps. Blood and spinal fluid Wassermann reactions were negative.

Gradual but complete recovery took place, with eventual return of the spinal fluid to normal. The patient was discharged, fully well, after 6 weeks.

Case 2 (Med. No. 17589).—M. E. L., a white female, aged 50 years, after a sudden attack of unconsciousness with right hemiplegia, remained comatose for 31 hours and was apathetic for the next 2 weeks.

Hemiplegia had disappeared by the 13th day, when the patient entered the hospital. Examination showed: temperature, 100.4° F.; pulse, 104;

tenderness of lumbar spine; blood pressure 196 systolic, 114 diastolic; sclerotic peripheral vessels; hyperactive deep reflexes suggestive right Babinski and Oppenheim.

Urinalysis: few red and white cells; trace of albumin; occasional granular cast. The blood count was within normal limits. The spinal fluid was xanthochromic after a small amount of old blood had settled out. Blood and spinal fluid Wassermann reactions were negative.

Recovery was complete and the patient was discharged in 3 weeks.

CASE 3 (Med. No. 18255).—H. S., a white male, aged 33 years, had severe pain in the left temple, plus sensations of "pins and needles" and heat and cold for 2 weeks, followed by sudden onset of delirium, convulsions and coma.

There was history of previous antiluetic treatment.

Examination showed: coma, alternating with delirium and convulsions; temperature, 99.4° F.; pulse, 128; blood pressure, 90 systolic, 60 diastolic; bilateral choked disk; slight ptosis of left eyelid; left facial weakness; protrusion of tongue to the left; rigidity of the neck; hyperactive patellar reflexes; positive Kernig; positive left Oppenheim and suggestive left Babinski. The pupils reacted to light and in accommodation, the right being larger.

The leukocytes were 15,200 per c.mm. Roentgen ray revealed no fracture of the skull. The spinal fluid was bloody (becoming xanthochromic on later taps). Wassermann reactions on blood and spinal fluid were 4+.

Gradual improvement occurred under antiluetic therapy and occasional spinal punctures. The patient was discharged completely well 15 weeks after admission.

CASE 4 (Med. No. 18306).—W. L., a white male, aged 41 years, after a 3-day alcoholic debauch fell unconscious when he attempted to get out of bed. Delirium alternated with coma the remainder of the day, and he was brought to the hospital that night, where examination showed the following relevant facts: temperature, 102° F. (rectal); pulse, 72; left pupil larger; no reactions of pupils to light; hyperactive deep reflexes; absent abdominal and cremasteric reflexes; bilateral Babinski.

The leukocytes were 15,400 per c.mm. The spinal fluid was bloody and became xanthochromic on later taps. Wassermann reactions on blood and spinal fluid were negative.

The pupils regained their normal reaction to light within the first week, and during the same time the deep reflexes on the right returned to a normal status, followed 2 weeks later by those on the left. Delirium was controlled by spinal punctures during the first 2 days, and was followed after that time by mental sluggishness which cleared up very slowly. The mental condition had just about reached normal when he was discharged at his family's request 6 weeks after admission.

CASE 5 (Med. No. 14413).—S. H., a colored male, aged 33 years, fell unconscious at work. Coma, lasting a few minutes, was followed by several hours of mental dullness. Then coma returned, with convulsions.

Examination showed: pulse, 120; blood pressure, 230 systolic, 90 diastolic; bilateral choked disk; deep reflexes absent.

The spinal fluid was bloody on the day of onset and xanthochromic 2 days later.

Convulsions became less frequent as the patient became weaker. The patient died 2 days after admission.

Postmortem examination (Forbus'[20] Case 7) showed diffuse hemorrhage over the surface of the brain, particularly at the base, and a ruptured aneurysm of the right anterior cerebral artery. The aneurysm showed no evidence of syphilis.

CASE 6 (Med. No. 17409).—J. P., a colored male, aged 42 years, had a left temporal headache 1 week before he suddenly lost consciousness while urinating. Coma lasted 1 hour and was followed by headache and diplopia. The patient had received an incomplete course of antiluetic treatment in the past.

Examination showed: temperature, 100; blood pressure, 120 systolic, 80 diastolic; enlarged epitrochlear nodes; left internal strabismus; left horizontal nystagmus; hypoactive deep reflexes.

Leukocytes were 11,100 per c.mm. The spinal fluid was xanthochromic. The spinal fluid Wassermann was negative, but the blood Wassermann was 4+.

The patient improved rapidly with spinal drainages and antiluetic treatment. Headache, strabismus and nystagmus disappeared and the patient was discharged 2 weeks after admission.

CASE 7 (Med. No. 17571).—E. N., a colored male, aged 42 years, had an attack of unconsciousness while in church, lasting for a few minutes and followed by sleepiness and headache.

Examination on entrance to the hospital 4 days later showed: pulse, 48; blood pressure, 240 systolic, 120 diastolic; deep reflexes hypoactive; otherwise negative, except for mental sluggishness.

Urinalysis showed: albumin +++; many white cells, hyalin and granular casts. There was moderate impairment of renal function as judged by the Mosenthal test. Blood counts were within normal limits. The spinal fluid was bloody, becoming xanthochromic on later taps.

Gradual improvement occurred. The pulse rate became normal, but the blood pressure remained elevated. The patient was fully recovered when he was discharged 6 weeks after admission.

CASE 8 (Med. No. 17820).—F. H., a colored male, aged 34 years, was found 2 days after disappearing from home. He was mentally confused and remembered nothing of the period of his absence.

Examination showed marked mental confusion and inability to answer even the simplest questions. The blood pressure was 245 systolic and 150 diastolic, and the examination was otherwise negative.

The spinal fluid was xanthochromic after old blood had settled out. Wassermann reactions on blood and spinal fluid were negative.

The urine contained a faint trace of albumin and an occasional hyalin cast for the first week and was negative thereafter. The nonprotein nitrogen was 62 on admission, gradually dropping to normal in 2 weeks.

The deep reflexes changed from a state of hyperactivity to hypoactivity and then became normal 2 weeks after admission. Mental confusion and dullness left very slowly. At the time of discharge, 9 weeks after admission, normal mental status had returned, but the patient was never able to recall the incidents of his 2 days' disappearance.

CASE 9 (Med. No. 14866).—H. W., a colored male, aged 35 years, had a frontal headache for a week which disappeared and returned in severer form 5 days later, causing him to seek hospitalization.

On examination he was found to have a temperature of 100° F. by rectum; pulse, 46; bilateral choked disks; slight ptosis and facial weakness on the right; biceps and triceps diminished; knee-jerks normal; peripheral vessels slightly thickened; blood pressure, 160 systolic and 100 diastolic.

Urinalysis: faint trace of albumin and occasional hyalin and cellular cast. Roentgen ray showed no skull fracture; ventriculogram revealed no evidence of brain tumor.

The spinal fluid was blood tinged and later became xanthochromic. Blood and spinal fluid Wassermann reactions were negative.

Two weeks after admission the pulse rate had increased to 76, the blood pressure was 140 systolic and 80 diastolic, and the abnormal neurologic

signs had disappeared. The patient was symptom-free and remained so until discharge, 5 weeks after admission.

CASE 10 (Med. No. 15367).—G. C., a colored female, developed headache; 4 days later, nausea and vomiting; and 6 days later, pain and stiffness of the neck.

Examination 9 days after the onset revealed stupor; blood pressure, 130 systolic and 96 diastolic; dilated, irregular pupils, the right being larger, reacting to light and on accommodation; painful, stiff neck; absent abdominals, normally active tendon reflexes.

Spinal fluid was bloody and, on later taps, xanthochromic. The blood Wassermann was 4+; the spinal fluid Wassermann, negative.

Improvement began on the 4th day after admission; abnormal symptoms and signs were gone in 2 weeks; and the patient was discharged perfectly well 3 weeks after admission.

CASE 11 (Med. No. 17199).—E. L., a colored female, aged 59 years, while hanging clothes on a line was seized with severe, lancinating pain in the back of the neck, accompanied later by vomiting, bitemporal headache and soreness in the lumbar region. When no improvement occurred after 2 weeks she entered the hospital.

Examination showed: temperature, 101.4° F.; pulse, 75; sclerosis of retinal vessels; moderately enlarged heart with systolic murmur at apex, transmitted over the precordium; tortuous, sclerotic peripheral vessels; blood pressure, 210 systolic, 120 diastolic; hyperextension and stiffness of neck; tenderness along spine; positive Kernig; adductor spasm of thighs; hypoactive deep reflexes.

Leukocytes were 23,800. The spinal fluid was bloody on admission and xanthochromic 5 days later.

Headaches ceased in a few days and the patient improved in other respects, until one day, about a month after the onset, she suddenly fell back unconscious. Coma lasted a few hours and was followed by bitemporal headache. Spinal fluid was again bloody and the leukocytes rose to 16,700 (having previously dropped to normal limits) on the 4th day after this second attack.

Gradual improvement began again and the patient was practically well, when she developed bronchopneumonia and died, 1 month after the second attack. Autopsy was refused.

CASE 12 (Med. No. 18290).—V. D., a white male, aged 41 years, developed severe throbbing headache, which subsided after taking capsules prescribed by a physician. The next afternoon, however, the patient's legs became gradually so stiff that he could not walk. There was no pain or swelling of the legs.

Examination showed an alert and coöperative patient; temperature, 99.6° F.; pulse, 80; blood pressure, 110 systolic, 70 diastolic; bilateral choked disk; positive Brudzinski; moderate stiffness of the neck; positive Kernig; hyperactive deep reflexes; no redness, heat, swelling or tenderness of the lower extremities.

Blood counts and urinalyses were within normal limits. The spinal fluid was xanthochromic. Blood and spinal fluid Wassermann reactions were negative.

The patient recovered rapidly so that he was free from signs and symptoms after 1 week and insisted on going home after 2 weeks.

Conclusions. The salient points revealed by this study of a small group of cases of subarachnoid hemorrhage are:

1. A variety of pathologic conditions may cause hemorrhage into the subarachnoid space.

2. The syndrome may present a wide variety of symptoms and signs.

3. In every case of coma of unknown origin, a diagnostic spinal puncture is imperative.

4. Headache is a prominent and sometimes the only symptom. A diagnostic spinal puncture is justified, therefore, in any case of unexplained headache.

NOTE.—The writer wishes to thank Dr. Thomas R. Boggs for permission to present these cases, and Dr. Boggs and Dr. Paul Padget for their advice and helpful suggestions.

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THE USE OF VARIOUS GASES IN ENCEPHALOGRAPHY.

A SUMMARY OF 210 CASES, USING THE SIMULTANEOUS DISPLACEMENT APPARATUS.*

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MOST workers in the field of encephalography have felt that the radiographic method of investigating the ventricular and subarachnoid systems after replacement of the cerebrospinal fluid with air would find much more extensive use in the study of the minor as well as the graver lesions of brain and meninges if the procedure could be made safer and less discomforting to the patient. For the past 11 years it has been the author's aim to obviate these two main

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deterrents to the more universal application of the encephalographic method. The present paper deals with the efforts in that direction, which have permitted the successful encephalography of 210 patients without fatality or serious accident.

TABLE 1.—CLASSIFICATION OF CASES.

			Cases.
A.—According to gases used.			
Air		Unfiltered	40
Air		Filtered	115
Carbon dioxid		Filtered	3
Nitrogen from	NH_4NO_2 (15); $NH_4Cl + NaNO_2$ (23); Commercial tank (2)	Filtered	40
Helium from	Commercial tank		12

B.—According to Clinical Diagnosis.	
No gross organic abnormality (psychosis, psychoneurosis, psychoasthenia)	57
Cerebrospinal lues	65
Vascular disease of unknown origin	16
Posttraumatic headache	15
Petit or grand mal	12
Encephalitis	9
Apoplectic hemiplegia	3
Obliterative subarachnoiditis	3
Congenital hydrocephalus	2
Brain tumors (not posterior fossa)	10
Posterior fossa tumors*	8
Cord tumors or adhesions*	10

* The relatively large number of cases of posterior fossa and cord tumors is due to the kind courtesy of Dr. E. J. J. King of Bellevue and Misericordia, Dr. R. A. Gerber of Harlem, and Dr. I. J. Sands of the Brooklyn Jewish, who felt that the use of the apparatus makes for added safety, and thus invited me to do some of their more difficult tumor cases at the respective hospitals.

Even as early as 1921 it was felt that the chief element of danger in the withdrawal of any appreciable amount of spinal fluid is the sudden alteration in the intracranial pressure. The danger appears to vary with the amount of fluid withdrawn before its equivalent in air is injected, being grave where the replacement unit is 20 cc., and much less serious where only 5 cc. is withdrawn at a time. The knowledge that the smaller the replacement unit the less the disturbance to the intracranial pressure prompted the development of an apparatus for the simultaneous (drop by drop) displacement of fluids by air or some other gas.[1,2]

The principle of the apparatus is that "fluid will seek its level," so that if the air to be injected is placed in a cylinder at a lower level than the spine, the inlet and outlet being connected with the subarachnoid spaces by lumbar puncture, making a continuous closed system, the cerebrospinal fluid will descend by gravity into the cylinder, and as it does so, an equivalent quantity of gas is forced out of the cylinder up into the subarachnoid spaces.

In the first 4 cases the spine was punctured in 2 interspaces, according to the method developed by Bingel;[3] the fluid inlet tube

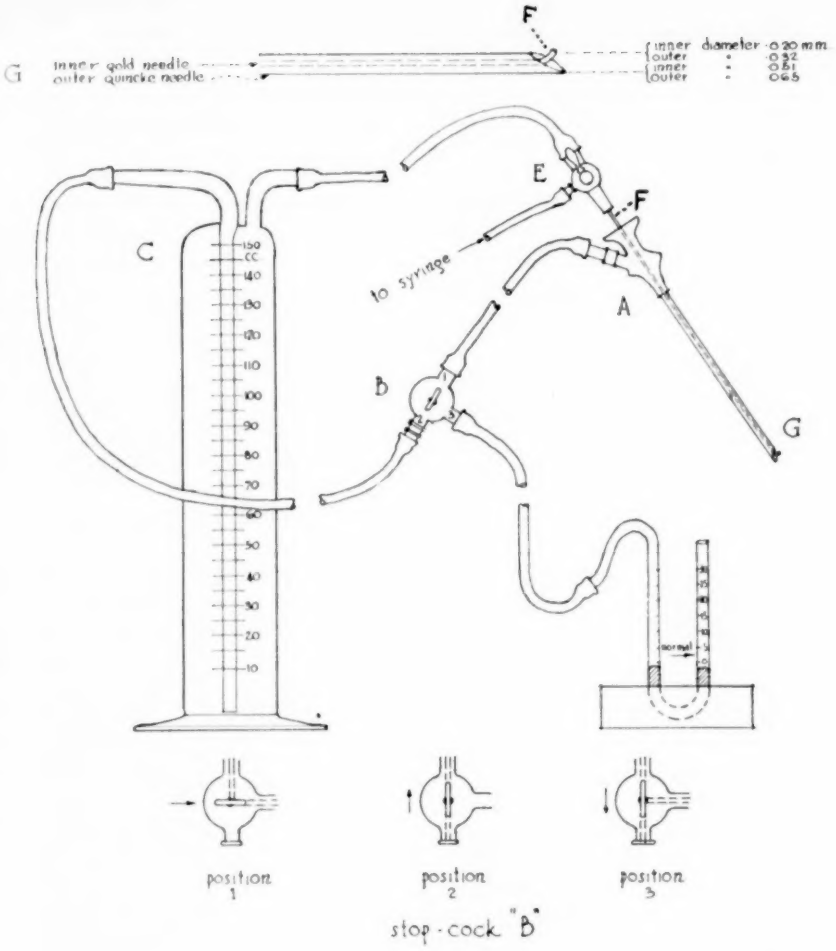
of the simultaneous displacement apparatus being connected to the lower puncture needle and the gas-conveying tube to the interspace above. To obviate the discomfort of the double spinal puncture a fine cannula was substituted for one of the needles and made to fit inside the other one, forming a "needle within a needle" unit that requires only a single lumbar puncture (Fig. 1). As such the apparatus was used in the succeeding 206 cases.

The writer admits that the use of the simultaneous displacement apparatus makes this method of encephalography manifestly less simple than the one generally employed now, the syringe and 2-way stopcock, where 5 cc. of fluid is withdrawn and an equivalent amount of air injected at a time. The factor of *added safety*, however, justifies its use in the mind of the author. The general mortality of encephalography is still quoted at 2 per cent.,[4] while by use of the simultaneous displacement apparatus the author has not had a single fatality in the 210 cases, 8 of which were posterior fossa tumors.

The second difficulty with encephalography, the reaction, consists of severe headache that occurs in almost every case. Occasionally shock supervenes, with its usual symptoms: vomiting, cold sweat, weak and thready pulse, and fall of blood pressure. The shock reaction in this series of 210 cases occurred infrequently and was at no time so severe as to require any treatment; the fall of blood pressure never being above 20 mm. of mercury.

The headache, however, is almost constant and baffles all attempts at circumvention. It is severe for 5 to 6 hours, and commonly lasts 1 to 4 days. It appears after the introduction of about 30 cc. of air and indicates absence of obstruction in the spinal canal, as well as the presence of the gas in the subarachnoid spaces over the brain, especially the frontal lobes. Sedative, such as chloral and luminal, and opiates such as morphin $\frac{1}{6}$ gr. in combination with hyoscin $\frac{1}{150}$ gr. are thus far the most promising methods of treatment for the headache.

It was thought at first that particulate matter in the injected air, such as dust, was responsible in part for the severe reaction. Therefore, in 115 cases the air was filtered through a water column before injection (Fig. 2). The headache during injection was the same as in the unfiltered cases, yet there seemed to be less severe reaction *after* the procedure than in the first 40 unfiltered control cases. At no time did we feel compelled to tap the spine for the relief of the post-injection symptoms. Nevertheless, for purely scientific purposes, spinal taps were performed 1 to 3 days after the injection of filtered air in 6 cases. The cell count was uniformly the same or even less than at the time of injection. This is to be contrasted with the pleocytosis that occurs after the use of ordinary injection methods.[5] It would appear then that filtration of the gas used in encephalography, although not of striking value in obviating the headache



SIMULTANEOUS · DISPLACEMENT · APPARATUS ·

FIG. 1.—THE SIMULTANEOUS DISPLACEMENT APPARATUS. The apparatus consists of a cylinder (*C*), with an inlet tube reaching to its bottom and connected to a spinal needle (*A*), and an outlet tube leading from the cylinder top to a fine cannula (*F*) made to fit inside the first needle. A mercury manometer is placed as a side-arm to the 3-way stopcock at *B* to measure the intraspinal pressure. The cylinder is kept at a lower level than the spine; the lumbar puncture is made; and the fine cannula is inserted snugly into the larger needle, the system thus becoming a closed one. As the cerebrospinal fluid descends through the large needle to the bottom of the cylinder it forces an equivalent amount of gas which it displaces from the cylinder up into the small cannula and the subarachnoid spaces. The speed of exchange of gas for fluid is controlled by raising or lowering the cylinder. The 3-way stopcock at *B* serves for pressure readings when turned to position 3, and for the usual working of the apparatus in position 2. Stopcock *E* is used to clear the air cannula in case fluid filled it, drawing up some gas from the cylinder (stopcock in position 1), changing to position 3 and injecting it into the spinal canal, then returning to position 2 for the usual exchange of gas and fluid. The detailed description of the apparatus and its workings can be found in the original article describing it (*quod vide*).

and other reactions, is to be recommended on the score of diminishing postoperative reactions, such as meningeal reaction and pleocytosis.

Another attempt at obviating the postinjection reaction was made about 5 years ago by the author, who felt that the reaction may be due not only to the mechanicophysical properties of the gas, such as its expansibility and solubility, but also to its chemical properties. This prompted the substitution of different gases for air in encephalography.

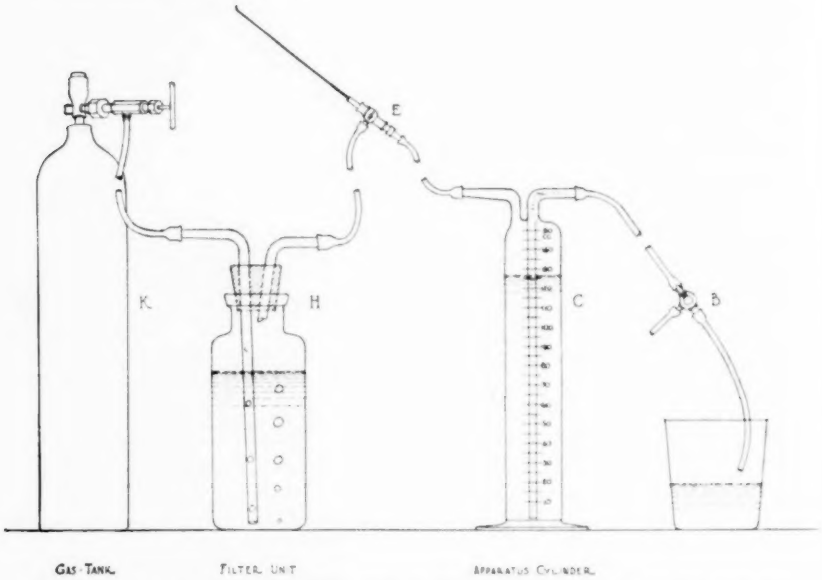


FIG. 2.—METHOD OF FILTERING THE GASES USED. The cylinder (*C*) and the accompanying tubing and stopcocks are filled with water and heated in the sterilizer for 20 minutes. The gas to be introduced (*K*) is filtered through a column of sterilized water (*H*), and is then allowed to displace the fluid in the cylinder, leaving about 0.5 cc. to act as a seal for the fluid-carrying stopcock, and as a gravity starter when the exchange of fluid and gas commences. The stopcocks are closed, separated from the filtering unit, and the apparatus is now ready for the replacement of the cerebrospinal fluid by the filtered gas contained in its sterilized cylinder.

When air is the gas used, the arrangement is exactly the same except that the tank is not present. The cylinder (*C*) which was previously filled with water and sterilized, is raised high, making the fluid in it flow out into the cup. This draws the air through the filtering unit (*H*) into the cylinder. The stopcocks are now closed, separated from the filtering unit, and the apparatus is ready for use.

In the first 3 cases carbon dioxid was tried. Because of its great solubility in spinal fluid, air had to be mixed with it. The calculation of the relative amounts of air and carbon dioxid necessary to maintain proper pressure relations after withdrawing the spinal fluid was so difficult as to make the method impossible. The reactions were severe and served to emphasize the necessity of using insoluble gases to replace the spinal fluid.

Nitrogen was then employed in 40 cases with more promising results. The gas was obtained by heating a small flask containing 5 gm. of ammonium chlorid, 5 gm. of sodium nitrite and about 20 cc. of water. The gases generated were led through a column of water, which acted as a filter, absorbing the ammonia that comes off in appreciable quantities, especially at the beginning of the heating. The filtered nitrogen was finally allowed to displace the water in the apparatus cylinder. (The nitrogen also can be prepared by heating an ammonium nitrite solution, or from a commercial nitrogen tank). Whichever way the nitrogen was prepared, the headache was found in almost all cases to be less severe than with air. The difference between nitrogen and air, however, cannot truthfully be said to be very striking.

Not satisfied with nitrogen, the author turned in the last 12 cases to the even more inert gas, helium, obtaining it, in pure state, at considerable expense from commercial cylinders. The helium was filtered through water in the same manner as the nitrogen. The headache in these 12 helium cases have been almost uniformly less severe than with the other gases. Although nothing definite can be said about helium as yet, the results are encouraging enough to suggest its continued trial use in the future.

It should be emphasized that the simultaneous displacement apparatus lends itself so easily to filling cavities by different gases that it served as the starting point and nucleus for the project of substituting different gases for air in encephalography. This reverts back to the original aim to make the apparatus a safe means of replacing the liquid in any closed body cavity by any other gas, or the gas in a cavity by any other liquid, either for diagnostic or therapeutic purposes. The apparatus not only enables one to drain off all the cerebrospinal fluid possible by substituting some gas for it, but permits the reverse procedure, the replacement of the gas injected into the canal by the patient's own cerebrospinal fluid, or any other fluid the therapist may desire, such as saline, serum, or medicated spinal fluid. It was the intention of the writer in 1924 to make use of this form of complete spinal drainage with gas replacement of the spinal fluid and redisplacement by medicated fluid or serum in cases of meningitis, following along the work of Sharp,[6] and in cases of cerebrospinal lues according to the work of Dercum[7].

In conclusion it may be said that whereas the question of safety in encephalography has been dealt with and met in great part by the simultaneous displacement apparatus, nothing substantial has been found to obviate the discomforting postinjection headache. The displacement of the cerebrospinal fluid by gases other than air holds a little promise for less severe reactions, but headaches of moderate severity are still present in almost every case.

Summary. 1. The use of the simultaneous displacement apparatus has permitted the encephalography of 210 cases without fatality or serious accident.

2. Filtration of the gases through water before injection reduces the postinjection reaction and obviates the pleocytosis that often occurs with unfiltered air.

3. The substitution of other inert gases for air in encephalography makes for less severe headaches. Helium appears more promising than nitrogen in this respect.

NOTE.—The author wishes to express his extreme indebtedness to Dr. C. H. Lavinder, Senior Surgeon, U. S. Public Health Service, without whose kind interest and invaluable suggestions throughout the past 11 years this work could not have been carried out, and to Dr. J. D. Reichard, Surgeon, U. S. Public Health Service, in charge of Neurological Service, Ellis Island and Staten Island hospitals, for his full coöperation clinically.

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NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.*

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SINCE the introduction of diphtheria antitoxin peculiar and sometimes fatal sequelæ to injections have been observed, the most common of which is serum sickness. At first reactions of this sort were attributed to antibodies in the serum. Within a year, however, Johannessen[1] had disposed of that assumption by demonstrating that reactions of similar character followed the injection of normal horse serum.

In 1911 Vincent and Richet[2] published an account of a man, aged

* Read before the Neuropsychiatry Section of the California Medical Association at the Sixty-first Annual Session, Pasadena, May 2–5, 1932.

30 years, who had received 10 cc. of tetanus antitoxin under the skin of the abdomen. Nine days later he suffered from repeated episodes of malaise, vomiting, urticaria, syncope, shock and anuria. Fifteen minutes after the second episode paresis of the right arm set in. Subsequently examination revealed atrophy of the right supraspinatus and paralysis of the serratus anterior with reaction of degeneration (R.D.). Since that time there have been many contributions of similar character, particularly in the French literature. My own interest in this subject was awakened by a case of this sort which I saw on April 17, 1930.

Case Reports. Case 1.—The patient was a man, aged 37 years, who had received a prophylactic injection of scarlet fever antitoxin in the lateral portion of the right arm 2½ months previously. Seven days after the injection the patient suffered from malaise, urticaria, abdominal cramps, fever and syncope. On the eighth day he complained of severe pain in both shoulders and within a few hours he noted weakness of the right shoulder. On examination there was almost complete flaccid paralysis of the right deltoid muscle and moderate weakness of the right biceps, brachialis, pectoralis major and scapular muscles. The right deltoid was rather tender and markedly atrophic. The right biceps reflex was not obtained; the triceps and supinator reflexes were normal. Sensation was intact throughout. On faradic stimulation of the right deltoid there was only a slight response from isolated bundles of the muscle. Eight months later the patient wrote that moderate improvement had taken place.

Through the courtesy of Dr. M. Stark, of Los Angeles, I recently had the privilege of examining a second case.

Case 2.—The patient was a man, aged 25 years, who had received 4½ months previously a prophylactic injection of tetanus antitoxin near the insertion of the right deltoid muscle immediately following a slight injury to the right thumb. On the third day the right arm was swollen, red and itchy. Six days later the swelling, erythema and pruritus, which had persisted, spread rather rapidly over the entire body. Coincidently the patient complained of excruciating pains through the shoulders and the pelvis. Two days later (11 days after injection of the serum) the erythema, swelling and pruritus subsided and the patient noted weakness of the right upper limb. The arthralgia persisted with diminishing severity for 1 month.

Examination revealed almost complete flaccid paralysis of the right deltoid and infraspinatus and moderate weakness of the right triceps and serratus anterior muscles. A few fibers of the anterior one-third of the deltoid could be contracted on effort. There was marked atrophy of the right deltoid and infraspinati and moderate atrophy of the serratus anterior. Over the lower two-thirds of the deltoid region there was partial anesthesia for light touch, superficial pain and warm and cold. The right deltoid, infraspinatus and serratus anterior showed partial R.D.

Review of the Literature. From the literature it has been possible to select 47 apparently authentic examples of neurologic complications of serum sickness which are presented in tabular form. Many of the reported cases, such as those of Etienne,[3] have been excluded because they did not belong to this category or because of inadequate

descriptions. Cases following the use of vaccines have been omitted. Engelmann's case,[4] often cited as the first to be recorded in the literature, is not included since there is no demonstrable relationship between the very mild serum reaction and the clinical picture of a slowly developing multiple peripheral neuritis which began 36 days later. In addition, I have excluded from consideration certain cases showing anaphylactic phenomena without serum sickness, such as that of Sheppe.[5] Because of the character of the clinical findings, the time relationships and the fact that mild cases of serum disease may be overlooked, 3 cases have been included in this series in which there are no definite data descriptive of serum sickness.

Analysis of the Cases. From a study of Table 1 it is apparent that males have been much more frequently involved than females. This may be attributed to the fact that men are more exposed to injuries necessitating prophylactic injections of tetanus antitoxin than are women. Of the 7 patients who developed neurologic complications following injections of diphtheria antitoxin, 4 were males and 3 were females. All of the patients in this series, however, who received scarlet fever antitoxin were males. That the disease occurs chiefly among adults is shown by the average age (26.9 years) of the group. To be precise, 33 of the 47 patients whose ages are recorded were 21 or more years of age.

TABLE 1.—NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.

Number of cases reviewed	49
Sex distribution:	
Males	44
Females	5
Average age in years (46 patients)	26.9
Average interval in days between first injection and onset of serum sickness (39 cases)	6.8
Average interval in days between onset of serum sickness and the neurologic complication (35 cases)	2.1

TABLE 2.—NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.

Serum injected	No. of cases.
Tetanus antitoxin	34
Diphtheria antitoxin	7
Scarlet fever antitoxin	5
Antipneumococcic serum, Type I	2
Antimeningococcic serum	1
Total	49

The average interval between the onset of serum sickness and the appearance of neurologic complications is difficult to determine accurately. In many instances arthralgia has been so severe as to be almost incompatible with physical effort. In the 35 cases, concerning which data of this sort are recorded, the interval was

approximately 2 days. In 13 instances the serum sickness seems to have been relatively mild, in 23 moderately severe and in 10 very intense. The average length of the serum disease in the 12 cases in which the duration was recorded, was approximately 3 days. From Table 2 it will be seen that 34 of the 49 cases developed evidence of neurologic complications following the injection of tetanus antitoxin. This is probably to be attributed to the fact that serum of this sort is most often given to adults who in turn are more likely to develop neurologic complications.

Apparently the brain, the spinal cord, the meninges, the nerve roots, the cords of the brachial plexus or the peripheral nerves may be involved directly by urticarial edema analogous to that in the skin. It has frequently been assumed that the urticarial lesion was located in one or more of the spinal foramina. Sicard and Cantaloube[6] suggested that certain cases of mononeuritis might be due to compression of a nerve as a result of an urticarial process within an aponeurotic sheath (neurodocitique).

In the majority of instances nervous structures associated with the brachial plexus have been involved (Table 3). In all of these cases there was disturbance of motor function; in about one-fourth of the cases there were sensory changes. The plurality of these cases showed involvement of the fibers derived from the fifth and sixth cervical nerves. To explain the unusually frequent involvement of the upper two nerve roots of the brachial plexus, Bourgignon[7] advanced the hypothesis that tetanus antitoxin selects nerves with low chronaxie while diphtheria antitoxin selects those with medium chronaxie. A casual analysis of the cases shows that this suggestion is untenable.

TABLE 3.—DISTRIBUTION OF THE NEUROLOGIC COMPLICATIONS OF 49 CASES OF SERUM SICKNESS.

Superior brachial plexus—unilateral motor	13
Mononeuritis (radial, 7; long thoracic, 1)	8
Optic neuritis	6
Brachial plexus—bilateral motor	4
Brachial plexus—bilateral sensorimotor	4
Superior brachial plexus—unilateral sensorimotor	4
Superior brachial plexus—bilateral motor	3
Superior brachial plexus—bilateral sensorimotor	3
Brachial plexus—unilateral motor	1
Brachial plexus—unilateral sensorimotor	1
C.N.S., meninges, brachial plexus—bilateral motor	1
Urticarial edema of the brain and meninges	1

Sainton[8] has pointed out that the process may not involve equally all fibers of a given muscle but may spare bundles of varying size. This was true in both of my cases. Profound changes in the electrical reactions, particularly in the distribution of the fifth and sixth cervical nerves are not uncommon.

TABLE 4.—ABSTRACTS OF 47 CASES OF NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS FROM THE LITERATURE.

Author.	Sex. Age.	Serum used.	Dosage.	Site of injection.	Serum reaction.		Evolution of neurologic complications.
					Days after injection.	Manifestations.	
Vincent and Richet, fils[2]	M 30	Tetanus, inject. 4 yrs. prev.	10 cc.	Under skin, belly	9	Mal., vom., u., sync., shock; repeated episodes with an.	15 min. after 2d episode, par., rt. arm; p., ser. ant. with R.D.; atr. of S.S.
Thaon: Rev. de méd., 1912, **32**, 749	M 30	Tetanus	10 cc.	....	9	E., u., tachycardia, oliguria; dur. 3 days	P. of ser. ant. with R.D., amy. beginning on 3d day.
Cauchois: Bull. et mém. Soc. de chir., 1912, **38**, 826	M 45	Tetanus	20 cc.	Right thigh	1	F., pr., arth., rt. shoulder	Par. and anes., dorsum rt. index finger and thumb; par. rt. upper limb; atr., triceps and I.S.; 18 mos. later residuals.
Dyke: Lancet, 1918, **1**, 570	M	Tetanus	750 U. 750 U. 500 U. 16,000 U. 16,000 U.	Right breast	13	2 days before last inj., pain, stiffness, rt. shoulder; dur. 4 days	Jan. 3: inability to abduct rt. arm. on 5th day; Mar. 9: atr. with R.D. rt. del., S.S. and I.S.
Halipré, Goujard: Normandie méd., 1920, **31**, 293	M 50	Tetanus	10 cc.	Left thigh	5	U.; gen'l'd pain; dur. 4 days	Same date: arth. rt. shoulder with drooping; winging, rt. scapula; atr., I.S. and S.S.
Marchal: Arch. méd. de belges, 1921, **5**, 406	M 22	Tetanus	10 cc.	....	..	....	On 8th day w., left shoulder and rt. arm; 2 days later drooping shoulders with p. of abductors of arm; later p. rt. serratus ant. and I.S. and S.S. bilat.
	M 23	Tetanus; prev. inj. at 8 yrs.	10 cc.	....	7	F., u., pr.; dur. 4 days	On the 4th day pain, both shoulders; inability to abduct arms; winged scapulæ, bilat. foll. by atr., trapezius and I.S. and S.S.; weakness, cricothyroid muscles; sensory loss over arms and scapulæ.
Mason: J. Am. Med. Assn., 1922, **78**, 88	M 25	Antipneumococcic Type I	200 cc. 100 cc. 100 cc. 100 cc.	Intravenously	8	F., 104° F.; gen'l'd rash	Hyperemia and swelling of optic disks 1 D.; e. of retina; veins engorged, arteries normal; restoration to normal in 3 mos.
	M	Antimeningococcic	...	Intraspinally	..	Gen'l'd serum sickness	Optic neuritis without visual disturbance; dur. 15 days; C.S.F., 15 cells.
	F 38	Antipneumococcic Type I	300 cc.	Intravenously	..	Gen'l'd serum sickness	Mild optic neuritis; C.S.F., 12 cells.

Mouriquand, Dechaume, Ravault: Lyon méd., 1923, **123**, 751.	F 34	Diphtheria antitoxin	20 cc.	Abdominal and gluteal muscles	4	F.; arth.; eruption with e.; dur. 4 days	On 3d day w. rt. area and shoulder, flexors, extensors, forearm; atr. del., I.S. and S.S.
Morichau-Beauchant: Arch. méd. chir. prov., 1923, **13**, 395	M 43	Tetanus	10 cc.	Inner aspect, left thigh	8	F.; marked u.; arth.	2 days later pain, upper limbs; next a.m., p., muscles both upper limbs with R.D. over r. distributions; dur. rt. 1 wk.; rm. 1 yr. later.
Sicard, Cantaloube[5]	M 55	Tetanus	20 cc.	Right thigh	9	Erythema, local e, pr arth.	2 days after onset, pain along r. n. foll. by comp. wrist drop, left.
	M 24	Diphtheria	20 cc.	Left flank	8	Erythema, u. and e., eyelids, face and limbs	On 3d day pain along left r. n. with comp. r. n. p.; biceps si. involved; dur. 18 mos.
	M 33	Tetanus	20 cc.	Left flank	8	Arth., erythema u. and e., face and glottis	On 3d day intense pain left arm foll. by typical r. palsy.
Lafourcade, Terris, Souques: Bull. et mém. Soc. méd. d. hôp., 1924, **48**, 757	M 29	Tetanus	10 cc.	Right thigh	6	U., beginning at site of inj., becoming gen'l'd; dur. 5 to 6 days	Toward end of serum reaction, w. upper limbs bilat. with atr. of shoulders, arms, forearm and hands; improvement.
Sainton, Descouts, Leclerc[5]	M 48	Tetanus; previous inj. 6 mos. ago	...	....	4	4 days after last inj. pain, shoulders; malaise, f. and e. of belly	Simultaneously w. upper limbs; fibrillary twitchings, triceps; partial R.D. rt. triceps; hypoexcitability, delt. and girdle muscles.
Lhermitte: La Practique méd. français, 1924, **1** 300	M 22	Tetanus	10 cc.	Under skin, abdomen	4	Arth., rt. shoulder	Winged scapula; later atr. musculature of shoulder girdle; improvement.
	M 23	Tetanus	10 cc.	....	9	Urticarial eruption with dyspnea	1 day later arth. rt. shoulder with p. abduction, arm and supination, forearm; atr. I.S. and S.S.
	M 22	Tetanus	10 cc.	....	..	....	W., del., I.S. and S.S. and biceps; winged scapula R.D.
André-Thomas: Presse méd., 1925, **33**, 217	F 26	Diphtheria	40 cc. 20 cc.	Buttocks	8	F.; u.; arth., esp. upper limbs; dur. 3 days	On 4th day inability to raise or rotate rt. arm; atr., rt. del., esp. post. 3d; diminished sensibility rt. 5th cerv. root area; loss, pilomotor reflex over anes. area.
Binet, Hoche: Rev. méd. de l'est, Nancy, 1925, **53**, 741	M 35	Tetanus	10 cc. 10 cc.	....	..	Arthralgia	Shortly, pain rt. scapular and biceps regions, left shoulder and arm; by 15th day unable to abduct arms; 6 wks. later atr. del., rhomboids, etc.
Brown: Am. J. Ophth., 1925, **8**, 614	M 12	Diphtheria	10,000 U.	Intravenously	..	....	Pinkish optic disks; hazy margin; hyperemia of retina with exud.; dur. 28 hrs.
	M 21	Diphtheria	10,000 U.	Intravenously	8	Fever, urticaria, pruritus	Optic neuritis; violent conjunctival reaction; dur. 28 hrs.

F., fever; w., weakness; p., paralysis; atr., atrophy; u., urticaria; arth., arthralgia; pr., pruritus; n., nerve; del., deltoid; S.S., supraspinatus; I.S., infraspinatus; r., radial; dur., duration; e., edema; bilat., bilaterally; par., paresis; inj., injection.

TABLE 4.—ABSTRACTS OF 47 CASES OF NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS FROM THE LITERATURE—*Continued*.

Author.	Sex. Age.	Serum used.	Dosage.	Site of injection.	Serum reaction.		Evolution of neurologic complications.
					Days after injection.	Manifestations.	
Leri, Escalier: Bull. et mém. Soc. d. hôp., 1926, **42**, 1468	M 38	Tetanus	10 cc.	Right buttock	5	F., arth., swelling at site of inj.	2 mos. later wife observed winged scapulæ; also had atr. rt. del. and lt. I.S. and S.S.
Faguet: Gaz. heb. d. Soc. méd., 1926, **46**, 404	M 25	Tetanus	10 cc.	Lat. surface, left thigh	9	Arth., lt. shoulder, neck and rt. upper limb	Next day flaccid p. upper limbs, lt. more than rt.; hypesthesia to touch, lt. upper R.D. extensors, hands, fingers; improv.
Verger, Aubertin, Delmas, Marsalet: Rev. de méd., 1927, **44**, 451	M 20	Tetanus	10 cc.	Subcutaneous	8	Pr. and e. at site of inj.; dur. 1 day; C.S.F. 30 lymph.	Following day pain, both shoulders, with p. both upper limbs, esp. rt., and abolition, tendon reflexes; winged scapulæ; atr., lt. biceps and I.S. and S.S.; hypesthesia both limbs R.D.; improv.
	M 25	Tetanus	20 cc.	....	6	E. of face; gen'l'd u.; dur. 2 days	Simult. gen. w.; impr. in 10 days but serratus magnus p. and I.S. and S.S. atr.
Faure-Beaulieu: Presse méd., 1927, **35**, 1419	M 52	Tetanus	...	Left thigh	12	U. at site of inj.	2 days later pain in all extrem.; subseq. p. rt. arm foll. by atr. and R.D. of del., S.S. and I.S.; zone of anes. dorsal aspect entire rt. upper limb.
Gordon: Med. J. and Rec., 1928, **127**, 330	M 9	Scarlet fever	250 U.	Left deltoid	2	F., u. at site of inj.; pr.	1 day later flaccid p., dist. r. n., reflexes dim.; sta. 3 wks.; later comp. recov.
	M 11	Scarlet fever	250 U.	Right deltoid	10 hrs.	Violent pr., entire rt. upper limb; burn. and ting. for'm.	Flaccid p., muscles innervated by r. 24 hrs. later; sta. 3 wks.; later com. recov.
Bourrat: Lyon méd., 1929, **143**, 787	F 22	Tetanus	...	....	..	E. and rubor pr.; headache	Orbital pain; amblyopia; central scotoma rt. eye; hyperemia of disk with venous engorgement; dur. 12 days.
	M 36	Tetanus	10 cc.	....	10	Pain, both upper limbs	W. extensors, wrists and fingers; 1 mo. later p. extensors of wrist and supinators; more marked, rt.
Kennedy[10]	M 15	Tetanus	...	Left arm	..	U., arth, swelling rt. arm	Par. of abduction, rt. arm; p., rt. serratus magnus on 9th day after inj.
	M 21	Tetanus	...	Left arm	7	Eryth. rash about site of inj.; arth., rt. shoulder	3 days later w., rt. shoulder and winged scapula.

	M 11	Scarlet fever	...	....	4	Fever, 104° F.; urticaria	Almost at once headache, menin. cry and retrac. of head; Kernig pos. bilat.; rt. homonymous hemianopsia, total alex. and jar. aphasia; partial rt. hemiplegia and aphasia; swelling, both optic disks; C.S.F. press. incr.; 14 lymph.; dur. 4½ wks.
	M 18	Scarlet fever	....	....	..	Fever, urticaria, arthralgia	Coincidently numbness with total anesthesia rt. circum. area; p., abduc. of arms with wasting, both del. and I.S. and S.S. bilat.; comp. R.D., del.; partial, scapular muscles; hypesthesia lt. circumflex area; improvement in 1 yr.
	M 12	Tetanus	....	....	..	Fever, urticaria, arthralgia	Inability to abduct arms; atr., both del.; decreased sensibility, both circumflex areas; incomp. R.D.; improv. in 6 mos.
Baudouin, Hervy: Rev. neurol., 1931, **1**, 306	M 10	Tetanus	10 cc.	....	8	U., next day transient trismus, pain in rt. shoulder	2 days later p. rt. serratus ant. and par. rt. trap.; partial R.D., affected muscles.
Bourgignon: Rev. neurol., 1931, **1**, 334	M 8	Tetanus	....	....	11	U., cervical rigidity, Kernig's sign, pain in neck and arms	Next day p., rt. arm; foll. day p. lt. arm and par. both lower limbs; 2 mos. later atr. p. rt. upper limb; par., lt. upper limb; bilat. Babinski; p. lt. abducens.
Wilson, Hadden: J. Am. Med. Assn., 1932, **98**, 123	F 77	Diphtheria	...	Right buttock	3	Arth. followed by swelling of hands	Gen'l w., r. arm; mod. atr., rt. S.S. and I.S. muscles.
	M 40	Tetanus	1500 U.	Anterior abdominal wall	6	Gen'l'd u.; 3 days later arth. and tingling and swelling feeling, fingers and wrist	3 days later arth. and tingling and swollen feeling, fingers and wrist; lt. impr. quickly; l., rt. grip; dimin. reflexes, lt. and absent reflexes, rt. upper limb.
	M 7	Tetanus	1500 U.	Left deltoid	7	Arthus' phenomenon; arth.	Lt. r. palsy, 1 day later; reflexes and sensation norm.; comp. recov. in 6 wks.
	M 17	Tetanus	...	Intramuscular, lt. thigh	6	Swelling, rt. knee and thigh with severe local reaction; arth., upper limbs for a fortnight	W., both arms, became apparent as pain disappeared; R.D. rt. del. I.S. and S.S. and lt. del.; analgesia and thermesthesia rt. axillary n. area.
	M 31	Diphtheria	...	....	10	Pain, neck to elbows, more severe, rt.	3 wks. later marked atr. rt. and sl. lt. del. with corresp. degrees of sensory loss over axillary n. areas.
	M 40	Tetanus	1500 U.	Left infrascapular	4	Hives for 2 or 3 days foll. by arth.	P. lt. del. I.S. and S.S. with R.D.; impr. 4 mos. later; comp. recov. 1 yr. later.
Young: J. Am. Med. Assn., 1932, **98**, 1139	M 40	Tetanus	1500 U.	Left deltoid	4	Erythema, vesicles, pr., e. and arth.; dur. 3 days	On 7th day w. of rt. arm.; atr. and R.D. rt. del. muscle; dimin. sensory distribution over rt. axillary n.

F., fever; w., weakness; p., paralysis; atr., atrophy; u., urticaria; arth., arthralgia; pr., pruritus; n., nerve; del., deltoid; S.S., supraspinatus; I.S., infraspinatus; r., radial; dur., duration; e., edema; bilat., bilaterally; par., paresis; inj., injection.

Fibrillary twitchings of the triceps were observed in the case reported by Sainton, Descouts and LeClerc.[9] There is matter for argument here as to whether the fibrillations were indicative of direct involvement of the cells of the anterior horn of the spinal cord or whether they were due to retrograde changes dependent upon damage to the anterior roots. Kennedy's case[10] showed evidence strongly suggestive of edema of the brain and meninges. Despite the severity of the symptoms and signs, most of the cases recover completely.

Comment. It is common knowledge that the incidence of serum sickness is intimately related to the amount of serum injected. In Weaver's series[11] 10 per cent of the patients receiving less than 10 cc. of serum developed serum sickness while 75 to 100 per cent of those receiving 90 cc. or more showed evidence of serum disease. Serum derived from certain horses is more likely to be followed by serum sickness than that obtained from others. Following the use of sera that have not been heated or that are less than 2 months old[12] serum sickness occurs with unusual frequency and severity. There is also a personal equation: individuals react differently following injections of serum obtained from the same source.

No data as to the relative frequency of the neurologic complications are available. It should be emphasized that while cases of this sort are of clinical and medicolegal importance, the occurrence of complications of such rarity should not be construed as a contraindication to the judicious prophylactic or therapeutic use of sera.

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CONGENITAL HEMIHYPERTROPHY: A REPORT OF EIGHT CASES.

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In 1926 one of us (E. W.) reported a case of congenital hypertrophy which involved the left part of the shoulder girdle, left arm and left hand. At that time, in the literature of the Surgeon-General's Library there was a total of 195 cases of congenital hemihypertrophy, 44 of which involved a whole side of the body. Since 1926 about 28 cases of the latter group have been reported.

An analysis of these cases from the literature gives the impression that the term congenital hypertrophy is used to denote a chaotic, bizarre syndrome, with but one constant feature; namely, increase in size of the involved parts. There is no reason to believe that this increase is compensatory hypertrophy. Usually there is no evidence that the enlarged part possesses greater strength or power, although the patient whose case was reported in 1926 felt that the involved part was the stronger.

The 8 patients whose cases form the basis of this report ranged in age from 3 to 32 years (Table 1). There were 5 males and 3 females. The right side was hypertrophied in 4, the left in 3, and in 1 the hypertrophy was crossed. The difference in the size of the extremities, as revealed by measurements, is often small, in fact it is usually less than it appears to be from general inspection of the patient. The most interesting case in this group, on account of its rarity, was that in which the hypertrophy was crossed (Case 8). There was no difference in the length of the arms and legs. The hypertrophy seemed to be mainly of the muscles. Consequently the disproportion in size was most conspicuous. The mental status was normal in 6 cases, 1 patient was mentally deficient, and the mentality of 1, who was mute, remained unknown. No history of congenital familial anomalies was obtained. Widespread congenital nevi were present in Cases 6 and 7. Case 1 presented 2 other congenital anomalies besides hypertrophy, namely, hypospadias and cryptorchidism. This child had also been suspected of having a congenital heart lesion at the time of his first visit to the clinic. This, however, had given no symptoms. A definite diagnosis of congenital heart lesion was made in Case 4. Cryptorchidism was also present in Case 7 and polydactylism in Case 4.

TABLE 1.—SUMMARY OF 8 CASES.

Case.	Age, yrs.	Sex.	Height, cm.	Weight, kg.	Hypertrophied side.	Difference in circumference of extremities, cm.				Difference in length of legs, cm.	Mental status.	Comment.
						Upper part of arm.	Lower part of arm.	Thigh.	Calf.			
1	3 7	M ..	87 125	14.0 25.0	Left ..	... 0.5	... 1.5	2.0 3.0	1.5 1.5	1.0 1.0	Normal	Hypospadias, cryptorchidism; questionable congenital heart disease; good general health.
2	4 9	F ..	.. 130	.. 15.0	.. Right	.. 2.0	.. 2.5	1.0 2.5	0.5 3.2	.. 2.5	Normal	Good general health.
3	9	M	115	20.0	Right	1.0	1.0	2.0	2.0	..	Unknown (mute)	Good general health.
4	14	M	147	41.7	Left	..	..	..	..	2.0	Normal	Congenital heart disease; polydactylism; orthopedic shoes fitted.
5	18	M	170	72.7	Right	2.5	3.7	7.5	1.3	..	Normal	Good general health.
6	23	F	165	58.0	Right	2.0	1.5	7.0	5.0	..	Deficient	Extensive nevus over body; good general health.
7	23	M	172	69.9	Left	2.0	2.0	10.0	6.0	..	Normal	Extensive nevus over body; hypertension, cryptorchidism.
8	32	F	153	60.0	Crossed	2.0	1.0	4.0	6.0	..	Normal	Left arm and right leg hypertrophied.

In Fig. 1 are given comparative measurements of size of corresponding parts on the two sides of the body. The differences in the ears, palpebral slits, nares, third fingers, and feet may be noted in the chart of Case 6. The photographs of patients (Cases 1 and 6) show the range of the hypertrophy. In Case 1 it would not be noticeable if it were not for the tilting of the pelvis, whereas in Case 6 it is obvious.

As a rule, obvious unilateral enlargement of a part or parts is of casual significance to a patient until something goes wrong. Difficulty in obtaining shoes and gloves to fit has caused little or no concern. With the patient who has become invalided on account of monstrous unilateral development, unequal growth has caused concern from birth; these are the unusual cases, which are similar to those first reported.

In a well-developed case of congenital hypertrophy, the resulting disproportion in development is grotesque. The hypertrophied parts often appear to "sag," are coarse, and lack symmetrical proportions in themselves. On the hypertrophied side there may be normal fingers and toes besides those that are hypertrophied. Crumpled toes, deformed from ill-fitting shoes, are mute evidence of the complaint that "the shoe on that foot has always been a little tight." The skin over the hypertrophied parts is normal in texture. There may be increased dimpling at the elbows, the distribution of the hair and other appendages of the skin is usually within normal

limits, occasional nevi may be present, and dentition on the involved side is precocious. Compensatory scoliosis and tilting of the pelvis in an attempt to compensate for the longer leg are common. If the compensation is not sufficient, limping and sciatica result.

The etiology is not known. The asymmetry begins in early embryonic growth and development. Phisalix obtained a 10 mm. human embryo which was asymmetric. Gessell has carefully reviewed the evidence which is in favor of the anomaly being a process of twinning. Many other hypotheses and suggestions have

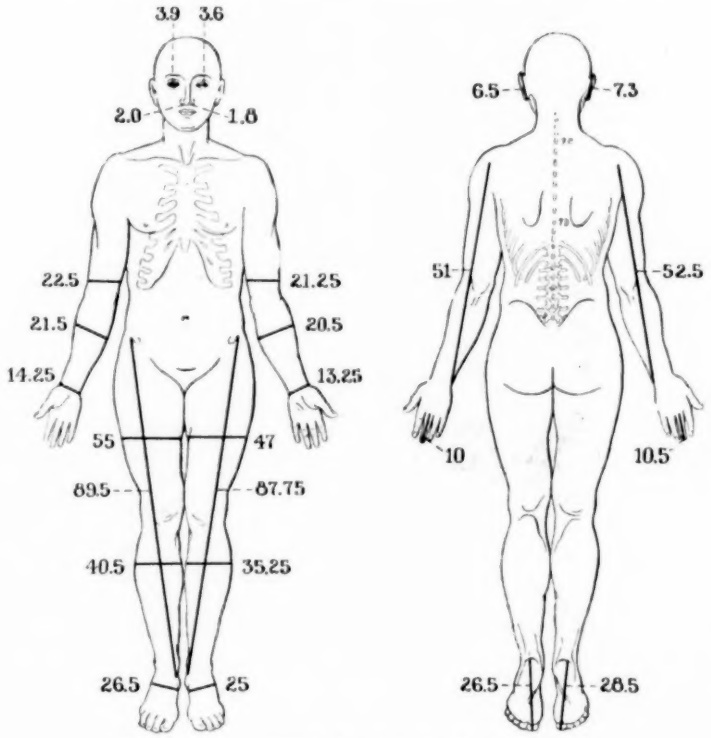

FIG. 1.—Diagrammatic drawing of patient in Case 6.

been offered, but none is more than a conjecture. Apropos of this, Jenkins once remarked, "The wonder is not that the two sides of the body are dissimilar, but rather, that they are ever alike."

A general description has been given. As to diagnosis, certainly if the hypertrophy occurs in the arm or leg, one must rule out congenital arteriovenous communication which is associated with enlargement of the part involved. Lymphedema is likewise eliminated without difficulty, since there is no edema, and if any doubt exists, a period of rest in bed, with elevation of the involved part,

should settle the question. The diagnosis should offer little difficulty if the possibility of hemihypertrophy is kept in mind, after careful neurologic examination to rule out hemiatrophy.

If the hypertrophied parts reach incompatible proportions in early life, the outlook for orthopedic correction is bad. Since the growth of the enlarged side continues throughout the period of normal development it may require correction in the second decade. Usually the anomaly does not cause discomfort.

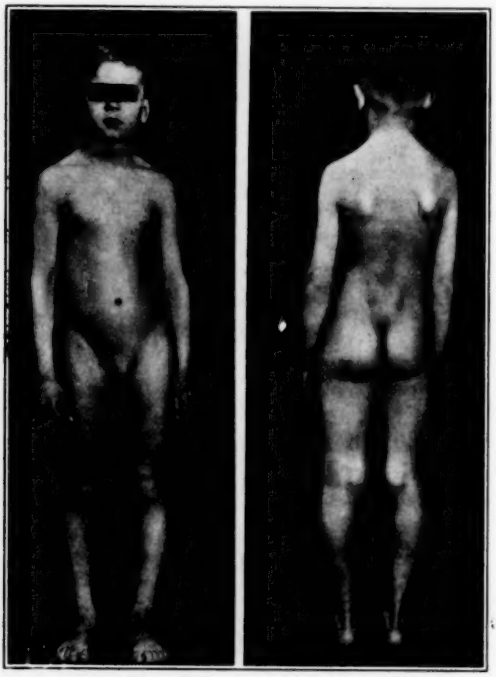

FIG. 2.—Photograph of patient in Case 1.

Case Reports. CASE 1.—This boy (Fig. 2), aged 3 years, was brought to the Mayo Clinic with the complaint that one leg was larger than the other. He also had pain in the knees. Birth had been normal, with a vertex presentation; labor, easy, and the birth weight, 7¾ pounds. The boy was breast fed for 1 year. He sat alone at 6 months, and walked and talked at 18 months. He was a "big, strong baby," and for the first year and a half he was perfectly well in every respect. Disproportion in the two sides of his body had been noticed some time before the age of 18 months; the left side was the larger. He had always been susceptible to colds. At 18 months he had an infection in the throat and a cutaneous eruption which was thought to be measles. At 2 years and 9 months he had a similar attack. At the age of 2 years the enlargement of the left side of the body was definite, and 10 months later he began to have pains in his knees, without swelling or stiffness. There was some restlessness and occasional crying at night.

The boy was well developed and nourished, alert, active and coöperative. The left side of the head and face was definitely larger than the right. The heart was not enlarged, and there were no thrills, but there was a loud systolic murmur well transmitted to the axilla. Hypospadias was present and the testes were not well descended; the right one was felt with difficulty. The left leg was definitely longer and larger than the right, and there was no edema. Reflexes were equal. Urinalysis, von Pirquet test, and roentgenograms of the chest gave negative results. The value for hemoglobin was 60 per cent, erythrocytes numbered 3,350,000, and leukocytes 4600 per c.mm. of blood. Examination of the nose and throat revealed fibrous tonsils of medium size.

Case 2.—This girl, aged 4 years, had been born at term, weighing 10 pounds. Labor had been moderately long but delivery normal. The child had been breast fed for the first 12 months, had her first teeth at 1 year, began to walk at about 10 months, and talked at 18 months. The mother noticed that when the child was 2 years old she limped. The left leg and left arm were smaller and shorter than the right. The limp gave no discomfort and did not interfere with motion. She ran and played without difficulty, having equal use of the two sides of the body. She never had paralysis, convulsions, or unconsciousness of any kind. Her general health was excellent.

The child was well nourished and well developed except that the right side of the body, and face, right leg and right arm were larger than the left. The pupils reacted normally, the tonsils were small, and the heart, lungs and abdomen were normal. Urinalysis, blood counts, estimation of hemoglobin, von Pirquet tests, and roentgenograms of the bones did not give evidence of anything unusual.

At the age of 9 years this girl was in good general health. Her right leg had continued to increase in length until she had difficulty in walking. There was marked scoliosis.

Case 3.—A boy, aged 9 years, had a family history which was entirely unimportant except for the fact that his mother had had two prematurely born babies. The patient had been born at 7 months, a twin, and had weighed 2½ pounds. He was bottle fed at first, then breast fed. He was weaned at 2 years, at which time he had had a severe illness with "spasms" and could not keep anything on his stomach. His condition gradually improved, and he had had no convulsions for 4 years before we saw him. From birth the patient's left side had seemed larger than the right.

The child was small for his age. His head was narrow in the bitemporal diameter and long in the fronto-occipital. The pupils reacted, and the thyroid gland was negative to examination. The first heart sound was indistinct, but the sounds were regular. The left foot was smaller than the right, and the left leg shorter than the right. Urinalysis, blood counts, estimation of hemoglobin, Wassermann test, von Pirquet test and roentgenograms of the chest were negative. Ophthalmoscopic examination disclosed normal fundi. Examination of the ears, nose, and throat disclosed complete deafness in both ears. Roentgenograms of the head revealed a normal sella turcica.

Case 4.—A boy, aged 14 years, was brought to the clinic complaining of lack of "pep," and of rheumatism. Birth and development had been normal except for polydactylism. He walked and talked at the age of 1 year and had his first teeth before he was a year old. He was in the eighth grade in school when we saw him. Aside from the enlargement of the left side of his body his general health had been considered good previous to the onset of the illness for which he was brought to the clinic. He was said to have had an attack of rheumatic fever of 6 weeks' duration 4 years before, and about 6 months after that his tonsils and adenoids had been

removed. Since that time he had limited his activities and had been very comfortable. In the 18 months before we were consulted he had had no "pep," his knees and feet had been sore, and there had been swelling of the ankles. The disproportion in the length of his legs had been corrected by special shoes.

The patient was well developed and well nourished. There was the appearance of slight fullness in the left side of the face and chest, and generally in the left arm and leg. The eyes were rather wide apart, which seemed to exaggerate the asymmetry of his face. The heart was not enlarged and its sounds were regular and clear. There were definite sinus arrhythmia and forced respirations. A loud systolic murmur was well transmitted to the axilla. Blood pressure was systolic 120 and diastolic 80. Urinalysis, blood counts, Wassermann test of the blood, von Pirquet test, Widal reaction, examination of ocular fundi, and roentgenograms of the teeth and sinuses gave essentially negative results. Roentgenograms of the cervical region gave evidence of a cervical rib on the right, and roentgenograms of the hands disclosed apparent developmental anomalies of both thumbs, marked dislocation of the phalangeal joint on the left, and anomalies of the metatarsal bone.

CASE 5.—A youth, aged 18 years, gave a family and past history not relevant to his complaint. His chief trouble was that his "left leg was too long" and ached when he walked; he had to lean to the right side in order to walk with comfort. There had been no other difficulty with the right leg, such as weakness, or pain in the hip or knee, and there was no swelling.

On general examination the patient appeared healthy. The left side of his face, and his left arm and left leg were developed out of proportion to the right. Strength on the two sides of the body was practically equal, and all motions of the joints were good. The pupils reacted normally. He had had much dental work, and the tonsils were small. The heart was not large, and there was a systolic murmur to the right of the sternum which was poorly transmitted. Blood pressures were systolic 155 and diastolic 88. The bones of the pelvis, and the femur, were reported normal. Urinalysis and Wassermann test of the blood gave negative results. The orthopedist gave him a pair of shoes which raised the heel of his right foot about 1½ inches. About 3 months later the patient returned and reported that he had received considerable relief.

CASE 6.—A woman (Fig. 3), aged 23 years, came to the clinic complaining of intermittent fronto-occipital headache and of difference in the size of the two sides of the body. From birth, the right side, including the face, right arm, and right leg had been larger than the left. This had not given her much concern and had caused no disability. She had been unable to finish the grade school. She had had pain in the right lower part of the abdomen and right thigh all of her life. For 6 years she had had headaches, which had been worse in the previous 2 years. There had been some blurring of vision associated with the headache. The family and past histories were negative. The patient had been married for 2 years without becoming pregnant.

The patient was well nourished; the right side of the face, the right arm, the right mammary gland, the right labia and the right leg were distinctly larger than the left. There was a large, flat, soft elevation on the right lumbar region 10 by 12 cm. A large superficial nevus was present over the chest and upper lumbar region. Neurologic examination revealed a mental age of 9 years according to Terman's revision of the Binet-Simon test. Mild secondary anemia was present. Urinalysis and the Wassermann test of the blood gave negative results. The basal metabolic rate was normal. Roentgenograms of the bones disclosed no differences in the two sides except in the pelvis, where there was lack of development of the left side.

CASE 7.—A man, aged 23 years, came to the clinic complaining of high blood pressure. Other members of the family were free of congenital defects or malformations. About a year previous to the patient's coming to the clinic, in his last year in college, he began to have pain across the front of his head. These attacks came every week or two and were accompanied by nausea and vomiting. The blood pressure was found to be elevated, and it was for a general survey of his condition that he came to the clinic.

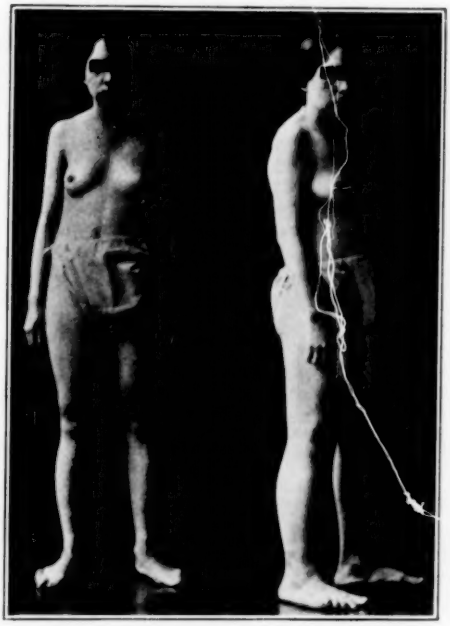

FIG. 3.—Photograph of patient in Case 6.

The patient's left leg and the left side of his body were larger than the right. There were extensive congenital nevi over the thorax. The pupils reacted normally, the heart measured 3 by 11 cm., and the blood pressure was systolic, 185; diastolic, 100. The lungs were clear. The right testis was undescended. General neurologic examination gave negative results, and results of laboratory tests were unimportant.

CASE 8.—A woman, aged 32 years, came to the clinic giving a family and a past history which were entirely without significance. She was married and had 2 normal children. Since the age of 5 years the *right* leg had been the larger, and for an indefinite period this also had been true of the *left* arm.

The patient was well developed and well nourished. The *left* arm and the *right* leg were decidedly the larger, but the face and the head were symmetrical. Blood pressure was normal, reflexes equal and active, and there was no edema. General neurologic examination, urinalysis, blood counts, and Wassermann tests, all gave negative results.

Summary. The 8 cases of congenital hemihypertrophy reported in this paper added to those that have been reported before make

80 cases recorded in the literature. Included in the 8 cases is 1 case of congenital crossed hypertrophy. Diagnosis is not difficult if the possibility of congenital hypertrophy is considered when there is unilateral enlargement of a part. The anomaly is often accompanied by other congenital or developmental features of note. The prognosis depends on the degree of hypertrophy and the age of the patient. After normal growth is finished, if there is no disability, there is no reason to expect any disability to occur.

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HYPOGLYCEMIC CONVULSIONS WITH HYPOPLASIA OF THE PANCREAS.

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The syndrome of hypoglycemia, not due to administration of insulin, was described by Harris,[1] in 1924. Since the appearance of his paper there have been many reports of cases in which the blood sugar has been found at low levels. According to the apparent etiology these fall into three groups: (1) Those cases in which there is a tumor of the pancreas involving the islets. Wilder, Allen, Power and Robertson[2] reported the first case of this kind. Carcinoma of the tail of the pancreas was found at autopsy. It was possible to prove the presence of insulin in the metastases from this growth. (2) Hypoglycemia in which exploration has shown an apparently normal pancreas. Finney and Finney[3] reported a case in which the removal of a portion of the pancreas was followed by clinical improvement. (3) Hypoglycemia attributed to other factors such as menstruation, functional or nervous disturbances and excessive carbohydrate intake. Anderson[4] reported a case in which there was an adenoma of the suprarenal gland. Harris[5] has recently given an excellent review of the American cases to date.

The patient with whom this report is concerned had prolonged hypoglycemia with the blood sugar rarely rising above subnormal levels. She had repeated convulsions and the operative findings

in regard to the pancreas apparently establish an additional possibility for hypoglycemic states.

Case Report. The patient, Mrs. R., aged 30 years, was referred by Dr. W. H. Bennett of Lamesa, Texas. She complained of attacks of weakness and her husband stated that practically every night she had a convulsion lasting from 10 to 30 minutes. She was well until the age of 13. At that time she became overheated and was sick for several weeks. At 15 her appendix and right ovary were removed. Following this at her menstrual periods she had "nervous spells" with uncontrollable jerking of the arms and legs. Her periods were regular, of the 28-day type, but scanty, lasting not more than 2 days. After marriage and the birth of her first child, she was well until the birth of her second child, at which time she had mastitis. Shortly thereafter, she began to have attacks of "blank spells." These lasted only a few minutes but were frequent. She then developed periods of weakness occurring late in the day or at night and 3 years ago lapsed into a stuporous condition which was more or less complete for 52 hours. Her physician correctly diagnosed this as hypoglycemia. The administration of glucose intravenously produced prompt recovery. He advised frequent feeding of sugar. This improved her condition somewhat.

She now does well during the daytime, but at night, most frequently at 1 or 2 A.M., she becomes restless, develops a cough, makes purposeless movements, and cannot be aroused. Salivation is marked at this time. If orange juice can be given, the attack is short, but at times it is impossible to induce her to swallow and in that case the attack may be prolonged and severe. Several times there have been severe convulsions with definite clonic spasms. At intervals, even when there are no convulsions, she complains of headache, drowsiness, and shows definite ataxic movements of hands and feet. She has been taking orange juice and sugar at frequent intervals but not during the night. Since the beginning of her illness she has gained 46 pounds (20 kg.), apparently due to the increased food intake.

Essential Physical Findings. Height 5 feet 2½ inches (159 cm.), weight 186 pounds (80 kg.), pulse 80, temperature 98.6° F., blood pressure 140 systolic, 92 diastolic. The eyegrounds showed no abnormality, the visual fields were normal, pupillary reaction normal. The heart and lungs were negative both by physical and fluoroscopic examination. Abdominal examination revealed no abnormalities; the liver was apparently of normal size. There was marked rectocele and cystocele and the left ovary was slightly enlarged. The nervous reflexes, both deep and superficial, were normal throughout.

Laboratory Findings. Blood: hemoglobin, 96 per cent; red cells, 4,520,000; white cells, 8600; polymorphonuclears, 72 per cent; Kahn reaction, negative; blood sugar (before breakfast), 48.5 mg. per 100 cc. This was not, strictly speaking, a fasting blood sugar since only 6 hours had elapsed since taking sweetened orange juice. The estimation of the blood sugar throughout was by the Folin and Wu method. The urine was negative. Roentgen ray study of the long bones showed no abnormalities; the sella turcica was perhaps slightly smaller than average but otherwise normal.

Subsequent Studies. The patient was sent to Baylor Hospital for further observation. The blood sugar was estimated shortly after a convulsion and was found to be 35 mg. per 100 cc. Blood-sugar readings were made at 4-hour intervals over a period of 24 hours and ranged from 40 mg. to 55 mg. per 100 cc. The curve for the 24 hours is shown graphically in Fig. 1. Isolated blood sugars were estimated after intravenous glucose or meals and the highest reading obtained was 105 mg. Glucose tolerance test was not done on account of the danger of producing subsequent hypoglycemic shock. The blood cholesterol was 139 mg. per 100 cc. Basal metabolic

readings were not made on account of the impossibility of preparing the patient properly. If sugar in some form was not supplied at 3-hour intervals by day and night, she had some evidence of an impending seizure.

Therapy. An attempt was made to reduce the carbohydrate intake in the diet and at the same time to supply her with small amounts at regular intervals. So long as the total available glucose was in the neighborhood of 200 gm. in the 24 hours, she was free from trouble, provided not more than 3 hours elapsed between feedings. When, however, the total glucose was reduced to 150 gm., it was impossible to prevent the attacks.

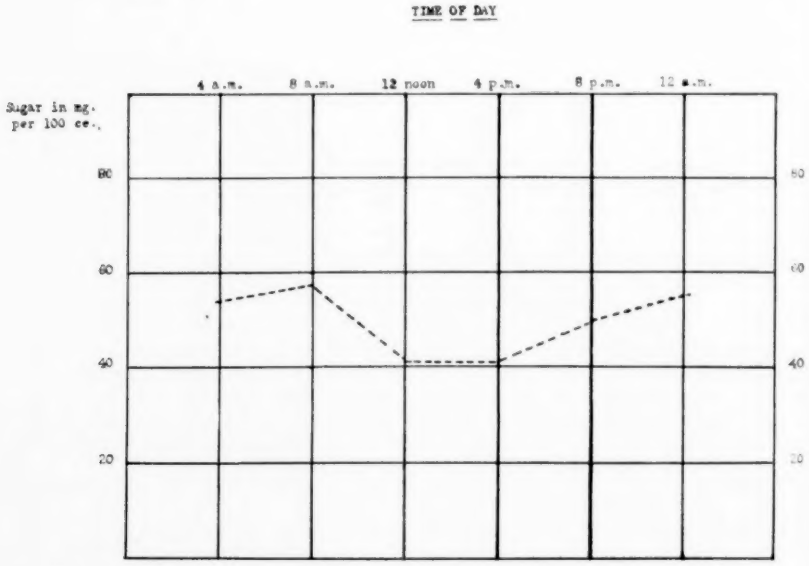

FIG. 1.—Blood-sugar curve for 24-hour period. The patient was receiving a total of 215 gm. of glucose in the diet during this period. The 8 A.M. reading is an interpolation from a previous day.

She was given thyroid steadily in the amount of 3 gr. (0.195 gm.) daily, without any appreciable effect upon her condition. Pituitary extract was given three times daily but proved to be of service only when administered in the presence of definite symptoms. Adrenalin was administered but once—this during a convulsion—and apparently had very little effect. It was not used more frequently for the reason that it was considered unwise to mobilize the glycogen reserve in the face of continued hypoglycemia.

Since medical treatment had little effect upon her condition, exploratory operation was decided upon. This was performed July 8, 1932, by Dr. W. E. Sistrunk. The pancreas was found to be about one-third normal size, being about 6 cm. in length and 2.5 cm. in width at the head. The tissue seemed friable but no evidence of a growth in the gland could be made out. A small piece of tissue was removed from the anterior central part of the body. No accessory pancreas could be discovered; the liver was apparently normal and nothing unusual was found in either kidney.

Dr. S. A. Wallace reported upon the tissue as follows: Specimen consisted of a small, red, friable portion of tissue, measuring 1 by 0.5 cm., cut with little resistance, was soft and slightly granular. Microscopic: Sections showed gland acini of normal size and appearance. The cells of the glands

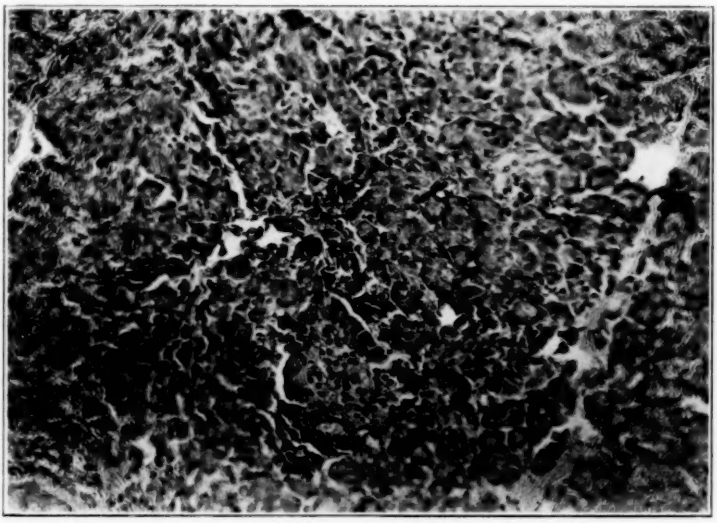

FIG. 2.—Microphotograph of tissue removed at operation, showing normal acini and islands.

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were regularly arranged with uniformly round nuclei. The islands of Langerhans appeared normal in number and in general were slightly smaller than normal. The cells were not abnormal in appearance. Connective tissue trabeculae were slender. There were no malignant changes seen in sections examined. Diagnosis: Practically normal pancreatic tissue.

The microscopic sections were also examined by Dr. George T. Caldwell, who confirmed the above findings. The appearance of the section is shown in the photomicrograph.

Postoperative Course. The patient stood the operation very satisfactorily and had little trouble for the first few days. It was noticeable that she was hungry and began to eat much earlier than would be expected following an operation of this type. By observation it was possible to predict when an attack was imminent. She complained of headache, drowsiness, and at times nausea. There was distinct tremor even before the patient was aware of any disturbance. Sugar given at this point usually but not always prevented further trouble. On the other hand, the injection of 0.5 cc. of pituitary extract hypodermically produced prompt improvement which lasted usually 3 to 5 hours. The final schedule for her care was based upon a diet in which the starches and sweets were held at as low a level as possible so far as the three daily meals were concerned. Sweetened fruit juice was given between meals, at bedtime, and every 4 hours during the night. With the appearance of any symptoms such as headache, cough, nausea, somnolence, or tremor, pituitary extract, 0.5 cc., obstetrical strength, was given immediately. The use of pituitary extract is based upon the work of Burn,[6] who found that the injection of this substance removed the symptoms of hypoglycemic convulsions and caused a rapid elevation of the blood sugar.

Discussion. This patient presented two symptoms which are not usually listed as those accompanying hypoglycemia. These were headache and cough. The relation of headache to other symptoms was constant. It was promptly relieved by the administration of sugar by mouth or glucose intravenously. In 1929 I reported a case of a man in whom headache developed regularly when the blood sugar fell to the low normal point of 73 mg.[7] The cough also seemed to be a regular accompaniment of the fall in blood sugar and was likewise relieved by the administration of sugar or pituitary extract.

As regards the possible causes for this patient's condition, the following may be considered:

1. *Overproduction of insulin* due to increased intake of food, particularly carbohydrates. The effect of increased carbohydrate intake in producing increased glucose tolerance has been suggested by John,[8] and Lennox[9] has shown that there is a definite stimulation of the blood-sugar mechanism of the body following the intake of glucose. This patient, however, increased her glucose intake upon the advice of her physician, following the development of her trouble, and her gain in weight was subsequent to this.

2. *Hypoglycemia due to endocrine disturbance:* While it was not possible to obtain an estimation of the basal metabolic rate, there was nothing in this patient's condition to suggest that she suffered from hypothyroidism. Her configuration was not that usually found in pituitary obesity and indeed, aside from the fact that her periods were scanty, there was no basis for assuming that any

endocrinopathy apart from that involving the pancreas was present. The abdominal exploration included palpation of the kidneys and liver but nothing was found in connection with these organs.

3. *Tumor of the pancreas*, particularly adenoma, could not be excluded entirely. As Smith[10] has noted, adenomas of the islands of Langerhans are fairly frequent but may be difficult to detect except by minute study. If such was present in this case, however, there was nothing to indicate it.

4. *Disturbance in the balance between the external and internal secretion of the pancreas:* There is evidence that a relationship exists between the external and internal secretions of the pancreas. Lueders and Watson[11] were able to show that the injection of insulin in patients with malnutrition produced a measurable increase in the concentration of pancreatic ferment recovered from the duodenum. Bensley,[12] in 1911, demonstrated hypertrophy of the islets together with degeneration of the acini after obliteration of the duct, and Mansfeld[13] found an increased sugar tolerance in dogs following ligation of the body of the pancreas. De Takáts *et al.*[14] found an increased sugar tolerance following division of the pancreas with electric cautery. They were unable to say whether the stimulation of the operation resulted in hypertrophy and hyperplasia of the islet tissue, whether there was an increase in insulin output, a change in the secretory rate as a result of change in innervation, or a functional liver block with diminished output of glycogen.

Terbrüggen and Heinlein[15] exposed the pancreas in rabbits to strong Roentgen ray treatment after isolating it and protecting surrounding organs. The rabbits died from hypoglycemic shock after 7 to 10 days. The pancreas showed degeneration of the excretory cells with little or no effect upon the islets. Since hypertrophy or hyperplasia of the islet tissue is not universally demonstrable following ligation of the pancreas or exposure to Roentgen ray, it seems possible that other factors may be concerned. Epstein and Rosenthal[16] found that the passage of trypsin into the blood stream of the pancreas neutralizes insulin and by passing into the portal circulation causes glycogenolysis with a consequent hyperglycemia. They concluded that no definite barrier exists between the structures which produce internal secretion and those concerned with the external secretion of the pancreas. They indicate the possibility that the internal flow of trypsin may be a part of the mechanism which regulates the supply and activity of the internal secretion of the pancreas. They also concluded that inactivation of insulin by trypsin may occur within the body of an animal under suitable conditions. This work has been confirmed by La Barre and Booleman,[17] who found that the products of acinar secretion, and particularly protrypsin in the blood supply of the islets, produces almost complete inactivation of insulin. It is a recognized fact that a relatively small amount of normal islet tissue may provide sufficient insulin for sugar metabolism. The idea may be advanced that the

small pancreas in this patient contained sufficient tissue capable of secreting a relatively normal amount of insulin. If ligation of the pancreas, obstruction of the duct, or other disturbances which cause atrophy of the acini may be assumed to act in some instances, by removing the inhibiting effect of acinar secretion it seems possible that the reduced amount of externally secreting tissue may have failed to provide an inhibiting effect upon the insulin. If this hypothesis is adopted, it is not necessary to assume that there was either overproduction of insulin (hyperinsulinism) or the release of abnormal insulin (dysinsulinism) in this case.

Concerning the use of the term hypoplasia, it must be admitted that this is not frequently encountered as regards the pancreas. In a personal communication Opie says: "There is no doubt, I think, that hypoplasia of the pancreas occurs and may affect the pancreas as a whole. . . . I assume that the term hypoplasia is applicable to a congenital condition in which one or all of the elements of the organ, although otherwise normal, are of abnormally small size or number." This term is applied to other organs which are below normal in size but in which the cellular structure is normal, hence there would seem to be no objection to its use in this case. The microscopic study of the section showed no evidence of cell degeneration or of fibrous replacement of tissue. Furthermore, since atrophy of the pancreas is frequently accompanied by diabetes, this would seem an argument against applying the term atrophy to the condition encountered in this patient.

Summary. A patient presenting convulsions together with a typical syndrome of hypoglycemia is reported. In addition, she showed two symptoms not usually included in the syndrome, namely, headache and cough. There was evidently hypoplasia of the pancreas. It is suggested that the hypoglycemia may be due to a disturbance between the internal and external secretion of the pancreas with a loss of the inhibiting effect of trypsin upon insulin.

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THE USE OF EPHEDRIN DURING SPINAL ANESTHESIA FOR THE RELIEF OF PARALYTIC ILEUS.

A THERAPEUTIC FALLACY.

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THE popularization of spinal anesthesia for the operative manipulation of somatic sensory areas has allowed the surgeon, without trepidation, to extend the usefulness of this procedure to the relief of paralytic ileus.[1,2,3] In the latter condition there is a complete cessation of intestinal motility, unassociated with mechanical obstruction and arising reflexly from some intraäbdominal condition. As demonstrated by Markowitz and Campbell,[4] the nature of paralytic ileus and the rationale of its relief through the employment of spinal anesthesia can be understood by a consideration of the scheme of sympathetic reflexes through the spinal cord. In Fig. 1 there is diagrammed the sympathetic reflex arc made up of an afferent fiber (*A*) which conveys sensory impulses from the abdominal parieties, an intercalated or connecting neuron (*B*) lying within the spinal cord, and an efferent fiber (*C*) which, being sympathetic in origin, will on stimulation lead to an inhibition of intestinal motility and to splanchnic vasoconstriction, the latter increasing the blood pressure. Under normal conditions, there being no potent stimulation of the sensory nerve endings in the parietes, there is no great inhibition of intestinal motility from this source. If, however, the peritoneum becomes inflamed or there is sensory stimulation of (*A*) by such an agency as a renal calculus or twisted ovarian cyst, a stream of impulses ascends the sensory fiber to set up a reflex stimulation of the motor path inhibitory to intestinal motility.

The treatment of paralytic ileus by spinal anesthesia aims to break up the integrity of the reflex arc at the intercalated neuron. As soon as the communication between the sensory and motor fiber becomes disrupted, intestinal contractions resume under the

influence of the vagus. At the same time, however, there is a fall in blood pressure due to the removal of the tonic vasoconstricting impulses which ordinarily flow through the sympathetic motor fiber.

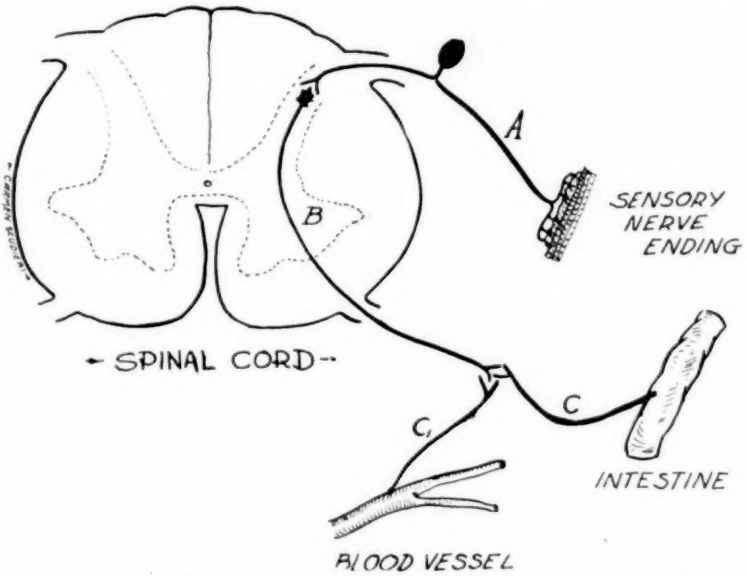

FIG. 1.—Diagrammatic representation of visceral reflex arc in thoracolumbar nervous system.

To counteract the hypotension accompanying spinal anesthesia, ephedrin is ordinarily used. The action of this drug is comparable to that of epinephrin in that it exercises its pressor effect by stim-

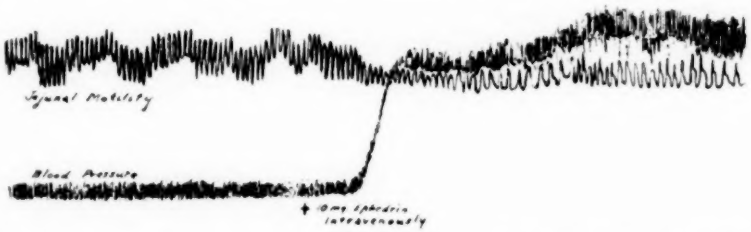

FIG. 2.—Effect of intravenously administered ephedrin on blood pressure and intestinal motility under spinal anesthesia.

ulation of the sympathetic myoneural junction. Since the inhibitory nerve endings in the intestinal wall are also sympathetic in origin, there is reason for assuming that ephedrin will inhibit intes-

tinal motility even during the course of spinal anesthesia. We therefore decided to determine experimentally whether such was actually the case.

Experimental.—Dogs under ether anesthesia were prepared for continuous tracings of blood pressure and intestinal movements. A three-way paraffined glass cannula was inserted into the carotid artery and connected with a citrate pressure bottle and a mercury manometer. An air-filled rubber balloon was inserted into the jejunum and connected with a chloroform manometer. After an adequate control record of blood pressure and intestinal motility had been secured, the dog was placed on its side, and 0.5 cc. of spinocain was administered intraspinally. The dog was then replaced upon its back, the head slightly lowered. After results were secured from this procedure, 10 mg. of ephedrin sulphate were given either subcutaneously or intravenously, and the effects noted.

Results.—In the 4 animals studied there was an absence of intestinal motility at the initiation of the experiment, presumably due to the peritoneal irritation attendant on opening the abdominal wall and the insertion and presence of the jejunal balloon. About 10 minutes after the introduction of spinocain, intestinal motility returned concurrently with a gradual fall in blood pressure. The administration of ephedrin caused a resumption of the original blood pressure level and an immediate cessation of intestinal motility (Fig. 2).

From the above results we believe the use of ephedrin as a pressor substance in spinal anesthesia, where the latter is initiated for the relief of paralytic ileus, to be contraindicated. These results are in harmony with the theoretical considerations which may also be advanced. It would seem logical that in the use of spinal anesthesia for this particular purpose, the use of ephedrin be dispensed with and, if the fall in blood pressure becomes alarming, recourse be had to some other method of maintaining it, such as the administration of physiological saline.

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ON THE ALLEGED ANTAGONISM BETWEEN DIGITALIS AND DIPHTHERIA TOXIN.

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The use of digitalis in the treatment of cardiac disorders occurring in diphtheria has been the subject of clinical controversy. The combined effects of digitalis and diphtheria toxin have also been investigated experimentally. Prejudice against the use of this drug in heart disease due to diphtheria has arisen mainly from the fact that the electrocardiographic changes resulting from diphtheria are similar in many respects to the effects of digitalis poisoning.[1] Haskell[2] found that a single dose of digitalis did not prolong the life of guinea pigs poisoned by diphtheria toxin, and obtained some indication that very large doses of digitalis were injurious. Edmunds and Cooper[3] found that the injection of digitalis into dogs severely poisoned by diphtheria toxin resulted in improvement of the circulation in acute experiments, although these dogs were more susceptible to digitalis than normal animals. In similar experiments on the cat Gold[4] found that even though diphtheria toxin had produced severe pathologic changes in the heart, the minimal average fatal dose of digitalis was the same as that for normal animals, but when the animals became moribund a marked increase in their susceptibility to digitalis appeared. These experiments confirmed the observation of Edmunds and Cooper that digitalis may stimulate the damaged circulation in poisoning by diphtheria toxin, and also served to explain the increased susceptibility to the toxin that was found in their dogs.

Recently there appeared a paper by Myers[5] in which the results of experiments on large numbers of guinea pigs seem to show a very striking protective action of digitalis against poisoning by diphtheria toxin. The author stated that the daily subcutaneous injection of digitalis for several days before or after the injection of the diphtheria toxin, protected guinea pigs almost completely against more than the fatal dose of the toxin, so that the animals failed to show symptoms of poisoning by the toxin and failed to develop the pathologic changes in the heart seen in animals that received the toxin alone. These results are exceedingly interesting because they attribute to digitalis a new action which has not hitherto been de-

scribed and which is apart from its action on the circulation, namely, that of a chemical antagonist to diphtheria toxin. Although Myers went far afield in stressing the application of these results to the toxemia of pneumonia in man, they would still be of considerable practical significance if they were applicable to diphtheria in man. It would not be possible to digitalize man or the cat without serious poisoning by the plan of dosage employed by Myers in guinea pigs, but the author attached great importance to such a plan of dosage in order to obtain the protective action of digitalis against the diphtheria toxin. In view of the striking results obtained by Myers, it was deemed desirable to investigate this matter in the cat, an animal which vomits from digitalis (the guinea pig does not vomit), and which in other respects has been shown to behave more like man in response to the digitalis bodies than do rodents. The results of this investigation form the subject of the present report.

Experimental. Experiments were carried out on a series of 66 cats. The analysis is based on the results obtained in 59 animals only, the others having been used for preliminary tests of the toxin or discarded because of infection or of abnormal behavior in the early part of the experiments. Of the remaining ones 29 received the toxin alone and served as controls for the other 30 which received the toxin in addition to digitalis for varying periods of time and in various doses.

The animals were kept in separate cages in a large room provided with ample sunlight and air. They were fed a diet of meat and water. Milk was sometimes used for testing the appetite, but was discontinued because it produced diarrhea. It was found that when the animals began to refuse meat, they usually also refused the milk. The animals were weighed daily and observations were made of the course of the poisoning. Postmortem examinations, especially for gross pathologic changes in the heart, were made in most of the animals.

A 4-ounce specimen of aged diphtheria toxin (undiluted) was obtained from the Department of Health of New York City on March 22, 1932. The last injection of this toxin was made on May 25, 1932. The specimen was kept on ice and from it a few cubic centimeters were taken when necessary for dilution, so that the original specimen was never removed from the ice chest for more than a few moments, nor was it exposed to the light. Fresh solutions were made up immediately before the injections in the case of each series. The toxin was injected intravenously in all except a few instances in which subcutaneous injections were given, and in most cases in dilutions of 1 to 100 or 1 to 200. The fact that in most instances a control group of cats received the same dose of diphtheria toxin of the same diluted specimen and at the same time as a digitalis series, served as a check on any possible deterioration of the toxin during the course of the investigation.

The effects of the diphtheria toxin were fairly uniform in most cases. After doses of 0.002 cc. of our specimen of toxin per kilogram,* the appetite was often found impaired by the second or third day; by the fourth or fifth day the animal frequently refused food completely, and a day or two before death it usually refused water as well. During the course of the poisoning there was sluggishness, drowsiness, weakness, nausea and vomiting, diarrhea (not due to milk), muscle twitching, partial paralysis usually of the hind limbs, although in a few cats also of the fore limbs, extreme weakness, prostration and death. In many cases death was attended by a convulsion and cessation of the heart in a manner that appeared similar to the effects of a rapid intravenous injection of digitalis. After 6 or 7 days in which the animal appeared ill, though still in fairly good condition, prostration frequently developed very rapidly, leading to death within a few hours or a day. The dose of 0.002 cc. caused death in all of 13 control animals on from the 5th to the 13th day. Larger doses of the toxin up to 0.1 cc. caused similar symptoms which came on much more rapidly. The duration of life after the administration of toxin varied from less than 18 hours to about 550 hours, depending on the dosage which ranged in these experiments between 0.1 and 0.001 cc.

The standard minimal lethal dose for guinea pigs (death of 250-gm. guinea pigs on the 4th day) of this specimen of toxin was 0.002 cc. This would be equivalent to 0.008 cc. per kg. Such doses caused death in cats in about 2 to 3 days (Table 2). In most of our experiments, however, we employed doses nearer to the absolute minimal fatal dose with the view of bringing out more strikingly any antagonism that might obtain between the toxin and the digitalis. It was not deemed feasible to use any smaller doses than 0.002 even though 0.001 cc. caused death (in 552 hours) because of possible complicating factors that might be introduced by excessively prolonged starvation. A dose of 0.0005 cc. was survived. After this dose anorexia and weakness appeared by the 5th day, but by the 8th day the animal began to improve and gain weight.

A tincture of digitalis, which was in use in a large cardiac clinic, and which proved to be very satisfactory clinically, was employed throughout this study. Its potency determined by one of us (H. G.) was 0.9 per cat unit. This was regarded as the average fatal dose. It was administered intravenously and in one group by stomach tube in varying percentages of this dose per kilogram of body weight.

Results. The results have been summarized in Tables 1 to 4, which compare the survival periods of the cats which had received injections of the diphtheria toxin alone with those which had received digitalis as well.

* All doses of toxin and digitalis were given per kilogram of body weight. Hence, for the sake of brevity, "per kilogram" will not be repeated.

In the first series of 11 animals (Table 1) the dose of toxin was 0.01 cc. (except in 2 of 6 controls which received 0.02 and 0.1 cc., respectively). Five of these received 1 large dose of digitalis (25 to 50 per cent of the average fatal dose) intravenously from 1 to 2 hours before the toxin. The digitalis caused vomiting in all but No. 7, 1 of the 2 which received the smaller dose of digitalis. All 11 animals died in about the same length of time.

TABLE 1.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Digitalis (per cent cat unit per kg., intravenously).
1	0.10	2 to 18	0
2	0.02	2 to 18	0
3	0.01	2 to 18	0
4	0.01	30 to 46	0
5	0.01	30 to 46	0
6	0.01	25	0
7	0.01	23	25
8	0.01	23	25
9	0.01	3 to 18	50
10	0.01	24	50
11	0.01	29 to 45	50

Animals No. 7 and No. 8 received the digitalis 2 hours before the toxin; Nos. 9 to 11, 1 hour before the toxin. The survival periods are stated in 2 numbers in cases in which the animal was found dead on the following morning, the first figure showing the period during which the animal was known to have been alive and the second the total interval up to the time it was found dead.

TABLE 2.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Degree of cardiac pathology.	Digitalis (per cent cat unit per kg., intravenously).
1	0.008*	48	...	0
2	0.008*	78 to 94	...	0
3	0.006*	29 to 45	...	0
4	0.005	41	...	0
5	0.005	45	+++	0
6	0.005	45	++++	0
7	0.005	50 to 66	++++	0
8	0.005	29 to 45	+++	66
9	0.005	29 to 45	++++	25+ 25
10	0.005	45	++++	25+ 25

* These 3 are the only cases in which the toxin was injected subcutaneously.

In a second series of 10 animals (Table 2) a longer period elapsed after the administration of digitalis before the toxin was given, and a smaller dose of the toxin was used, 0.005 cc. in all except in 3 of the 7 controls. To 1 animal (No. 8) 66 per cent of the average fatal dose of digitalis was given intravenously 2 days before the toxin. This induced vomiting. Each of 2 others (Nos. 9 and 10) received 25 per cent of the average fatal dose of digitalis intravenously on each of 2 successive days. The second dose caused vomiting in 1 of these (No. 10). The toxin was administered on the day follow-

ing the second dose of digitalis. None of the 3 animals had shown any toxic signs of digitalis action when the diphtheria toxin was injected. All 10 animals showed similar symptoms of diphtheria poisoning, and all died. Those receiving digitalis did not live any longer than the controls, and the gross pathologic changes in the hearts were indistinguishable in the two groups.

In a third series of 6 animals (Table 3) a still smaller dose of diphtheria toxin was given, 0.003 cc., and larger doses of digitalis were given intravenously in fractions at intervals of several hours before the toxin. No. 4 received 4 doses of 25 per cent of the average fatal dose each, 29, 5, 4 and 3 hours, respectively, before the toxin. No. 5 received 3 doses of digitalis of 50, 25 and 25 per cent of the average fatal dose, 5, 4 and 3 hours, respectively, before the toxin. No. 6 received 2 doses of digitalis of 50 and 25 per cent of the average fatal dose, 5 and 4 hours, respectively, before the toxin. In all 3 vomiting was produced by digitalis, the first 2 having been tolerant animals, because emesis did not occur until after an average fatal dose. All 6 of this series of animals developed typical symptoms of diphtheria poisoning, and all died. Those receiving the very large doses of digitalis died somewhat sooner than the controls. Such large doses of digitalis were not used again because of the possibility that they themselves might cause death.

TABLE 3.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Digitalis (per cent cat unit per kg., intravenously).
1	0.003	146 to 162	0
2	0.003	121 to 137	0
3	0.003	146 to 162	0
4	0.003	73 to 91	25 + 25 + 25 + 25
5	0.003	26	50 + 25 + 25
6	0.003	164 to 180	50 + 25

It is generally accepted that one large dose of digitalis exerts essentially the same cardiac actions as the same intensity of digitalization with smaller doses over a long period of time. Large doses given for a short time before the toxin in our experiments were without antagonism to diphtheria toxin, and since Myers stressed the importance of prolonged treatment with digitalis in his guinea pigs, in order to elicit the antagonism we carried out the largest series of experiments in cats with more prolonged digitalis administration. In these, also the smallest dose of toxin was used. Each of 32 cats received 0.002 cc. toxin (Table 4) and of these 13 (Nos. 1 to 13) served as controls while 19 received digitalis for varying periods of time before and after the toxin. The exact dosage and intervals were not the same in every case because it was aimed to maintain a state of full digitalization by small daily doses.

When sufficient cumulation occurred in any case to cause loss of appetite or vomiting, the dose was withheld for 1 or 2 days and then its administration was resumed. When the animal became ill from

TABLE 4.—SHOWING EFFECT OF PROLONGED DIGITALIZATION IN ANIMALS RECEIVING SMALLEST DOSE OF DIPHTHERIA TOXIN, 0.002 CC. PER KG.

Animal No.	Duration of life, hours.	Degree of cardiac pathologic change.	Digitalis dosage (per cent cat unit per kg. daily).
1	218	+?	0
2	149 to 163	++++	0
3	195 to 211	−	0
4	196 to 212	+?	0
5	217	+++	0
6	144 to 160	++	0
7	217 to 233	+?	0
8	314 to 330	+?	0
9	172	++++	0
10	189	++	0
11	100 to 116	+?	0
12	168 to 184	+++	0
13	100 to 116	++++	0
14	144 to 160	++	50, 0, T
15	96 to 112	+?	50, 0, T-20
16	45	++	50, 0, T-20
17	94	+?	50, 0, T-20
18	198 to 214	+?	25, T-20, 0, 0, 0, 0, 0, 10, 0, 0, 10
19	198 to 214	++	25, 0, T-20, 0, 0, 0, 0, 10, 0, 0, 10
20	264 to 280	+++	25, 0, T-20, 0, 0, 0, 0, 10, 0, 0, 10
21	212	++	25, 0, T, 0, 0, 0, 0, 10, 0, 0, 10
22	168 to 184	+?	25, 0, T-20, 0, 0, 0, 0, 10
23	116 to 232	++++	20, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 0, 20
24	310 to 312	+?	10, 10, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 0, 20, 0, 0, 0, 10
25	312 to 328	+?	10, 10, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 0, 20, 0, 0, 0, 0, 10
26	168 to 186	++++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 0, 0, 0, 0, 10, 10
27	69	++++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10
28	96 to 114	+++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10
29	96 to 114	+	20, 20, 0, 5, 0, 10, 10, T-10, 10
30	48 to 66	++	20, 20, 0, 5, 0, 10, 10, T-10, 10
31	192	+++	20, 20, 0, 5, 0, 10, 10, T-10, 10, 0, 0, 0, 0, 10, 10
32	192 to 208	++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10, 0, 0, 0, 0, 10, 10

The digitalis was injected intravenously in all cases except in Nos. 26 to 32, to which the drug was given by stomach tube.

See Table 1, footnote, for the significance of the 2 numbers under the "Duration of Life."

The line of figures under "Digitalis Dosage" lists the doses of digitalis given on consecutive days from the beginning of the experiment up to the last injection. "T" represents "toxin," and the figure after it, the dose of digitalis given on the same day.

Under the "Degree of Cardiac Pathologic Change" are listed estimates of the amount of gross cardiac damage as indicated in most cases by the size and number of gross hemorrhages in the heart.

the diphtheria toxin it frequently vomited, and this was difficult to distinguish from digitalis overdosage. In some of these cases the digitalis was withheld for a few days in order to avoid the danger of killing the animal with digitalis. In most instances vomiting had occurred from digitalis before the toxin was administered. In no instance was the animal appreciably depressed from the digitalis before the toxin was given.

The experiments in this series fall into four groups: The first group (Nos. 14 to 17) received 1 large dose of digitalis 2 days before the toxin and a smaller dose on the day the toxin was given (except in No. 14 in which there was still some anorexia 2 days after the first dose of digitalis). Most animals of the second group (Nos. 18 to 22) received 1 large dose of digitalis 2 days before the toxin, a smaller dose on the day of the toxin administration, and in all but 1 case 2 smaller doses subsequently. The animals of the third group (Nos. 23 to 25) received digitalis during a period of 9 to 10 days up to the day on which the toxin was injected, at which time an additional 30 per cent of the fatal dose was given to insure full digitalization. One or 2 additional doses of digitalis were given during the course of the diphtheria poisoning after a sufficient interruption to insure that the animal would not be suffering from digitalis poisoning. In all of the above 3 groups the digitalis was given intravenously. In the 4th group (Nos. 26 to 32) it was given by stomach tube, the figures in Table 4 indicating percentages of the intravenous average fatal dose. These animals received digitalis up to the point of anorexia, nausea or vomiting during a period of 7 to 9 days prior to the toxin injection and then from 2 to 4 additional maintenance doses of digitalis during the course of the poisoning by diphtheria toxin.

An examination of the survival periods and the degree of gross pathology in the heart in the 13 control animals of this series and the 19 treated with digitalis by these various methods shows no evidence of antagonism. Not one of the digitalized cats lived longer than the longest survival period of the controls, while several of the cats receiving very large doses of digitalis showed survival periods much shorter than the shortest periods of the controls. It appears, therefore, that very large doses of digitalis hastened their death.

Most of the hearts showed numerous areas of hemorrhage in the mural pericardium and endocardium, varying in size from that of a pinhead to about 0.25 cm. in diameter. As seen in Table 4, these were similar in the controls and treated animals.

Comment. As we have already mentioned, the present study on the cat was suggested by the very striking results obtained in guinea pigs by Myers, working in Dixon's laboratory in Cambridge. These results seemed to show practically complete protective action

by digitalis against fatal doses of diphtheria toxin in guinea pigs. Our results with 59 cats show, on the contrary, that digitalis does not protect this animal in the slightest degree against diphtheria toxin, and that very large doses hasten its death.

Myers appears to have been interested in the problem of digitalis in pneumonia. He spoke of the lack of general agreement as to the value of digitalis in pneumonia, and cited among other papers several statistical studies of war data which recommended the use of digitalis, but made no reference to the only systematic and controlled statistical studies of this subject in large groups of patients that had ever been made, namely, those of the Pneumonia Committee[6] of Bellevue Hospital in New York City, which included an intensively studied series of about 1000 patients and covered a period of nearly 3 years. The data obtained in these studies leave little doubt that the routine use of digitalis in pneumonia does not lessen the mortality and give some indication that it may increase it. Myers stated: "The primary object in devising and carrying out this investigation was to determine whether in acute pneumonia digitalis could be regarded as a life-saving remedy, and to this I think I give a clear answer in the affirmative." It is well to bear in mind that this conclusion is based not upon observations with a "toxin" of pneumonia in patients, but with the toxin of diphtheria in guinea pigs, and that our experiments have shown that in the cat —an animal which behaves more like man in response to the digitalis bodies—digitalis exerts no protective action against diphtheria toxin.

Summary. Our results show that digitalis does not afford any protection against poisoning by diphtheria toxin in the cat. It is probable that the same is true in man. Results obtained with diphtheria toxin in guinea pigs had been used as a basis for the statement that "in acute pneumonia digitalis could be regarded as a life-saving remedy." This assumption is unwarranted and has received no support from systematic statistical studies which show that the routine use of digitalis in pneumonia does not lessen the mortality.

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ACUTE ANGIOSPASTIC RETINITIS: OCCURRENCE IN CASES OF SEVERE HYPERTENSIVE AND RENAL DISEASE.*

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Although the clinical distinction between chronic glomerulonephritis and diffuse vascular disease such as malignant hypertension is usually definite, cases are occasionally seen which present some of the characteristics of both conditions. Also, in a given case observed at different times the preponderance of evidence of diffuse vascular or renal pathologic processes may change a good deal as the disease progresses. The appearance of the ocular fundi is frequently a very important aid in the distinction between the two conditions, although this picture also may change considerably with the development of the disease.

In the course of cardiovascular renal disease 3 types of retinitis occur which present sufficiently characteristic ophthalmoscopic appearances to permit of rather accurate diagnosis of their etiology. The retinitis of severe essential hypertension, the retinitis of malignant hypertension and the retinitis of chronic glomerulonephritis have features which enable the observer to distinguish them readily in most instances. In a certain number of cases a form of retinitis occurs which is not typical of any of these 3 groups, and which is best classified ophthalmoscopically under the general term of acute angiospastic retinitis.

The diffuse or localized edema, the flame-shaped or round hemorrhagic areas and the cottonwool patches which appear as acute processes in the retina in the course of the various types of cardiovascular renal disease are probably of angiospastic origin. The punctate hemorrhages and areas of degeneration which are based on organic occlusion of arterioles or capillaries are apparently of more gradual onset, and of more chronically progressive course and are usually localized to single areas of the retina (retinitis of arteriolosclerosis). Lesions based on organic closure of retinal veins or larger arteries are likely to be of sudden onset, but they present aspects readily distinguished from those of diffuse retinitis.

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In the average case of severe hypertensive disease a tendency to recurrent relatively localized angiospasm is manifested by the appearance in the retina from time to time of scattered cottonwool patches and hemorrhagic areas. In such cases sclerosis of the arterioles is always present. In the more fulminating types of hypertension, diffuse retinitis, with edema of the disks, is frequently seen. This type of retinitis also is usually engrafted on visible sclerosis of the arterioles. In acute or subacute glomerulonephritis angiospastic retinitis can occur which is similar to that of severe benign hypertension except for the normal appearance of the walls of the arterioles. In the terminal phases of chronic glomerulonephritis diffuse retinitis occurs when arterioles have previously been normal, and is often angiospastic. Acute angiospastic retinitis without visible arteriolosclerosis or localized angiospasm, although it always occurs in association with elevated blood pressure, is then not characteristic of primary hypertensive disease, but from the ophthalmoscopic standpoint alone is always more suggestive of primary diffuse glomerulonephritis. It has been demonstrated to occur, however, when the primary condition, as proved by the other clinical and laboratory manifestations and by the subsequent course of the disease, is a diffuse disease of the arterioles throughout the body.

The characteristics of acute, diffuse angiospastic retinitis are generalized, marked attenuation of the retinal arterioles with or without irregularity of their lumina, diffuse edema of the retina, relative ischemia at times, with mild edema of the disks, cottonwool patches, hemorrhagic areas and, in the later stages, punctate exudates of residual edema and partial star figures in the macular regions. In most cases it is impossible to determine that actual or organic disease of the walls of the arterioles is present. The arterioles in these cases do not show the exaggerated reflex and definite, sharply defined indentation of the walls characteristic of the slowly developing sclerosis of hypertension, and arteriovenous compression is not present. The points of excessive narrowing of caliber are irregularly distributed, are of varying extent and usually are marked by some haziness of the perivascular retina. In a few cases recent or organized thrombi have been seen in small arterioles, and have been considered by us as strong evidence of active disease of the intima. Such findings in the retina denote diffuse disease of the arterioles. The type of acute angiospastic retinitis here described among men and nonpregnant women is essentially similar to the retinitis seen in toxemia of pregnancy. If the patient lives beyond the acute stage of the disease the retinitis may have one of several outcomes. It may heal completely, leaving only the signs of past retinitis, mild pallor of the disks with increased connective tissue, residual perivascular thickening and perhaps mild pigmentary proliferative changes in the retina and choroid. It may result in

chronic obliterative disease of the arterioles, retinitis of arteriolosclerosis. It may gradually assume the characteristics of malignant hypertension (Group 4 as described by Keith), with definite sclerosis of the arterioles and gradually increasing edema of the disks. The course of the retinitis is often but not invariably indicative of the course of the general disease. If the retinitis ends in complete healing the primary disease probably has been glomerulonephritis, and the patient may recover or go on to chronic glomerulonephritis. If the retinitis develops into the arteriolosclerotic type hypertension of the severe essential type is the usual outcome. If the retinitis assumes the malignant type the patient will have rapidly progressive hypertensive disease.

Case Reports. CASE 1.—A man, aged 38 years, was admitted to the Mayo Clinic April 11, 1929, complaining of severe, continuous frontal headaches of 9 weeks' duration. They were relieved by lying down and aggravated by rising. He had had scotomata since the onset of headaches. For 6 weeks previous to admission he had noticed some impairment of vision. He complained, also, of urinating once or twice at night. He had had slight dyspnea for about a year. For 6 or 8 years he had noticed some puffiness of the eyelids at intervals.

Vision was 6/60 in each eye. The pupils, reflexes, and peripheral visual fields were normal. Ophthalmoscopic examination revealed acute angiospastic retinitis, without any definite sclerosis of the arterioles. Venous stasis was marked, and considerable edema and hemorrhagic extravasations were present in the retina. The tonsils appeared to be infected. The lungs were normal. The area of cardiac dullness extended 3 cm. to the right and 10.5 cm. to the left of the midsternal line; a systolic murmur was heard at the apex and at the base; the second sound at the aortic area was accentuated, graded 1. There was peripheral sclerosis, graded 2. The blood pressure in millimeters of mercury was 210 systolic and 125 diastolic. The liver was palpable.

Laboratory Tests. The specific gravity of the urine was 1.010, albumin was graded 3, there was no sugar, erythrocytes were graded 3 on one occasion, and on the same occasion a few pus cells were seen. Excretion of phenolsulphonephthalein after intravenous injection was 40 per cent in 1 hour. In the dilution test the lowest urinary specific gravity was 1.002. *Blood:* Hemoglobin, 18.7 gm. per 100 cc.; erythrocytes, 4,400,000, and leukocytes 5000 per c.mm.; urea, 86 mg. per 100 cc. (this was reduced to 53 mg. by the time of dismissal) creatinin 3 mg. per 100 cc.; CO_2 combining power 68 vol. per cent; chlorids 618 mg. per 100 cc. A serologic test of the blood for syphilis was negative. An electrocardiogram showed left ventricular preponderance.

Histologic study of the arterioles in a small piece of pectoralis major muscle removed for biopsy revealed definite but rather inconstant changes. The average ratio of wall to lumen was 1 to 1.6, but individual ratios varied from 1 to 0.9 to 1 to 2 (normal 1 to 1.7 to 1 to 2.7). The maximal changes were noted in arterioles from 50 to 100 micra in diameter. The nuclei of the cells in the media of the arterioles were more than normally numerous; the intimal nuclei appeared normal. There was moderate tortuosity.

Three weeks following admission of the patient there were definite macular stars in the ocular fundi and moderate arteriolosclerosis of postretinitic type. The retinitis simulated that of glomerulonephritis in its character and course, because of the absence of definite sclerosis of the arterioles. The marked variations in ratio of wall to lumen of the various arterioles

seen in the specimen of muscle removed for biopsy suggested that only part of the arteriolar bed had suffered organic injury, but that the disease was quite widespread. In spite of the condition of the retina, the clinical picture suggested hypertension rather than renal disease.

A diagnosis was made of early malignant hypertension, arteriolosclerosis and tonsillar sepsis. We learned that this patient died February 1, 1930.

CASE 2.—A man, aged 31 years, was admitted to the clinic October 27, 1930, complaining of blood in his urine and swelling of his ankles. In April, 1930, he had had a sore throat for a day. Two weeks later he noticed blood in his urine which persisted for several days. May 20, some edema developed involving the face, ankles, and lower part of the back; on several occasions he vomited. On the advice of his physician he remained in bed for 3 weeks on a diet low in protein and salt. Following this, the edema was much decreased, but it had increased slightly afterward, which was noticeable when he was up and about. July 27, tonsillectomy had been performed. For 9 weeks preceding registration he had been in bed. During this time his physician found albuminuria and elevation of blood pressure. In addition, occipital headaches were occasionally present. When ambulatory, there was occasionally frequency of urination. Two years previous to his admission his blood pressure was found to be elevated in the course of an examination for insurance. He had no subjective disturbance of vision.

The patient's face was puffy and pale. Vision was 6/4 in each eye. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed acute angiospastic retinitis, with evidence of commencing resolution. The retinal arterioles showed marked attenuation but sclerosis was not definitely visible. The peripapillary retina was mildly edematous and cottonwool patches and hemorrhagic areas were present. All these changes were more marked in the left eye in which there was also a partial macular star. The lungs appeared to be normal. The area of cardiac dullness extended 2 cm. to the right and 14 cm. to the left of the median line, the heart tones were clear, there were no murmurs, and the aortic second sound was accentuated, graded 1. Peripheral sclerosis was graded 1. The blood pressure, studied over a period of 24 hours, showed a systolic range of 150 to 210 and a diastolic range of 90 to 150 mm. mercury. Edema of the thoracicolumbar region was graded 1, and of the ankles graded 1.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 3, there was no sugar, hyalin casts were graded 1 to 2, granular casts graded 2 to 3, erythrocytes graded 1 to 2, and pus cells varied from occasional cells to cells graded 2. *Blood:* Hemoglobin, 12 gm. per 100 cc.; erythrocytes, 3,900,000 and leukocytes, 10,000; urea, 40 mg. per 100 cc.; creatinin, 2.1 mg. per 100 cc.; CO_2 combining power was 51.3 vol. per cent; phenolsulphonephthalein excretion, 35 per cent. A serologic test of the blood for syphilis was negative. In the dilution test the lowest specific gravity was 1.006; in the concentration test the highest specific gravity was 1.022. An electrocardiogram showed left ventricular preponderance. A roentgenogram of the head indicated slight increase in intracranial pressure.

A small piece of pectoralis major muscle was removed for biopsy. The maximal changes were seen in the smallest arterioles (from 15 to 50 micra in diameter where the average ratio of wall to lumen was reduced to 1 to 1.1), there was moderate involvement of arterioles from 50 to 100 micra and less involvement of arterioles larger than 100 micra. In the smallest arterioles the medial nuclei appeared normal, but those of the intima were increased in number and tended to be polygonal. The arterioles were not tortuous. A diagnosis was made of subacute glomerulonephritis, arteriosclerosis, and cardiac hypertrophy. The edema disappeared during the period of rest in the hospital. At the time of dismissal the patient was advised to follow a salt-free diet of 40 gm. of protein, 2500 calories, with

fluids to the amount of 1000 cc. daily. Ferric citrate, grains 15, 3 times a day, was prescribed.

March 19, 1931, the patient returned to the clinic for observation. He had been feeling well and complained only of cramps in the calves of the legs at night at intervals during the 2 weeks previous to admission. Examination of the ocular fundi showed that the retinitis had improved considerably. The retinal arterioles were still moderately attenuated, but did not show definite sclerosis. The edema had subsided except for a few residual punctate exudates in the left macular region. One small hemorrhagic area was present in the left retina. The disks were slightly pale. The area of cardiac dullness extended 2 cm. to the right and 13 cm. to the left; the second aortic sound was not accentuated. Peripheral sclerosis of the rubbery type was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 120 to 170 and a diastolic range of 60 to 110 mm. mercury. The specific gravity of the urine was 1.018, albumin was graded 3, there was no sugar, hyalin casts were graded 1 and granular casts graded 2, erythrocytes graded 1 to 2 and pus was graded 1. *Blood:* Hemoglobin, 10.3 gm.; erythrocytes, 3,720,000, and leukocytes, 11,300; urea, 122 mg.; creatinin, 5.4 mg.; cholesterol, 303 mg., and serum proteins, 5.5 gm. per 100 cc., and the return of phenolsulphonephthalein was slight. In the dilution test the lowest specific gravity was 1.008, and in the concentration test the highest was only 1.014. A roentgenogram of the head was negative.

A piece of muscle removed for a second biopsy at this time showed an average ratio of wall to lumen of 1 to 1.2; this change was again chiefly in the small arteries. The nuclei of the intima were less prominent than before, but one arteriole contained a definitely organized thrombus. A diagnosis was made of chronic progressive glomerulonephritis with at least temporary subsidence of the active involvement of the arterioles, and secondary anemia. April 9, 1931, the patient reported that his ankles had become somewhat swollen. We learned that this patient died February 9, 1932.

The appearance of the retinitis at the first examination suggested the presence of primary nephritis (probably subacute glomerulonephritis) rather than primary hypertensive disease. The course of the retinitis, its rather rapid healing without the development of definite sclerosis of the arterioles, further supported this view. The degree of change in the ratio of wall to lumen noted in the arterioles of the pectoralis major muscle is greater than one would expect in an ordinary case of glomerulonephritis, and disproportionate to the changes observed in the arterioles of the fundus. We believe that such changes are evidence of the widespread organic disease of arterioles which can occur in certain cases of glomerulonephritis. From the clinical standpoint, a diagnosis of glomerulonephritis seemed most likely. This corresponded well with the ophthalmoscopic observations.

Case 3.—A man, aged 33 years, was admitted to the clinic August 24, 1931, with a complaint of pain in the back of the neck, weakness and shortness of breath. In 1918 he had had a severe attack of influenza following which he did not feel as well as formerly. Seven years previous to admission he commenced to have frontal headaches which were characterized by a feeling of pressure inside the head and accompanied by vomiting that resembled the projectile type. The headaches usually lasted for about 6 hours, and occurred about 3 or 4 times a year until 2 years preceding admis-

sion, after which they occurred about once a week. Four months previous to admission he had had another attack of influenza followed by steady aching pain in the neck posteriorly which continued to trouble him. Albuminuria was found at the time of the onset of the headaches. For a year preceding admission, weakness, vertigo and dyspnea had developed after exertion. In the morning he also noticed puffiness beneath the eyes and in the fingers. He did not complain of disturbance of vision.

Central vision was approximately normal, but was not accurately tested as the patient was seen in bed at the hospital. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed residual angiospastic retinitis. The disks were full, somewhat blurred, and rather pale with some proliferation of connective tissue. A few punctate exudates of residual edema were present in the retina. The arterioles were narrowed and the retina around them appeared to be thickened. Sclerosis, graded 2, was present, but was mainly of secondary, postretinitic type. The lungs appeared to be normal. The heart was enlarged, graded 2; there was a faint apical systolic murmur, a basal systolic murmur, and the pulmonic sound was greater than the aortic second sound. Peripehal sclerosis was graded 1. The blood pressure studied over a period of 24 hours showed a systolic range of 140 to 200 and a diastolic range of 88 to 140 mm. mercury.

Laboratory Test. The specific gravity of the urine was 1.010, albumin was graded 4, there was no sugar, and erythrocytes were graded 2. *Blood:* Hemoglobin, 12.1 gm. per 100 cc.; erythrocytes, 3,760,000 and leukocytes, 6000; urea, 54 mg. The return of phenolsulphonephthalein was 45 per cent. A serologic test of the blood for syphilis gave negative results. The electrocardiogram showed left ventricular preponderance, diphasic *T* wave in Lead II and inverted *T* wave in Lead III.

A diagnosis was made of chronic glomerulonephritis with diffuse vascular disease, marked hypertension, and secondary anemia.

The fact that the retinitis in this case had probably been of short duration, and that it had healed without leaving characteristic arteriolosclerosis, suggested that it had been associated primarily with glomerulonephritis. The presence of a moderate grade of arteriolosclerosis, even though not typically hypertensive, would indicate, however, definite organic injury to the systemic arterioles which might warrant the diagnosis of primary hypertensive disease, or at least glomerulonephritis with secondary vascular injury. The long history of albuminuria with headaches and vomiting was more suggestive of glomerulonephritis. This was in accord with the findings in the fundi.

Case 4.—A man, aged 35 years, was admitted to the clinic October 27, 1931. In April, 1929, he had strained his back when at work. Two weeks later he noticed hematuria, which continued for a period of 2 weeks. Two months later severe intermittent pain commenced in the right lumbar region and radiated anteriorly. Laparotomy was performed elsewhere a short time later. The abdomen was said to be full of blood, and the right kidney was low and was punctured. The blood was removed and no further treatment was given. The patient made a good recovery, except that he urinated once or twice at night. The systolic blood pressure at that time was 240. For a year previous to admission he had had occipital headaches in the morning, and some impairment of vision. The nocturia had increased. During the 2 weeks preceding admission he had noted hematuria again. There was nothing further of significance in the history except that at the age of 29 he had had scarlet fever.

FIG. 1.—Case 4. Recent thrombosis of a small superior nasal arteriole.

FIG. 2.—Organized thrombus with complete obliteration of a small superior temporal arteriole.

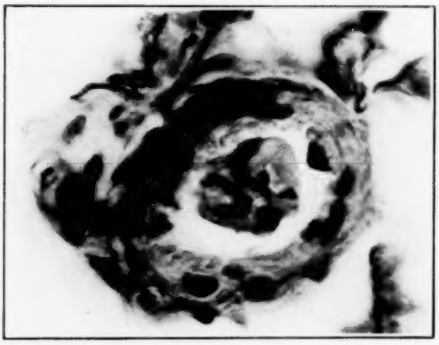

FIG. 3.—Case 4. An arteriole from the pectoralis major muscle removed at biopsy (× 675); partial occlusion by organized thrombus may be seen.

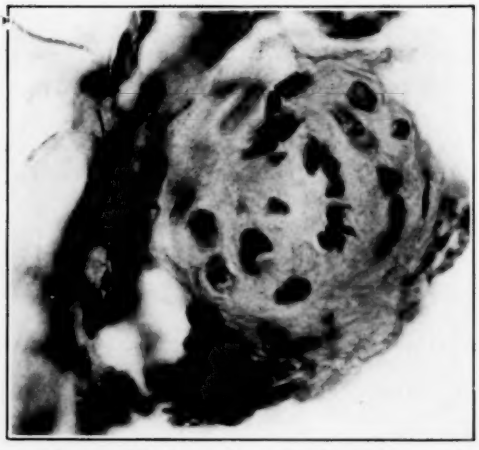

FIG. 4.—Case 4. An arteriole from the pectoralis major muscle; an increase in number and size of nuclei of the intima and media and almost complete obliteration of the lumen may be noted.

Vision of the right eye was 6/20 and of the left, 6/7. The pupils, reflexes and peripheral fields of vision were normal. Ophthalmoscopic examination revealed angiospastic retinitis in the stage of commencing resolution. The disks were slightly pale. The peripapillary retinæ was mildly edematous. Scattered cottonwool patches and hemorrhagic areas and incomplete macular stars were present in the retina of both eyes. The arterioles were moderately attenuated and irregular. The sclerosis, graded 2, was not typically hypertensive, but the presence of recent thrombosis, not yet organized, in one small arteriole in the left retina suggested the existence of active disease of the intima. The examination of the lungs gave negative results. The area of cardiac dullness extended 2 cm. to the right and 10 cm. to the left of the midsternal line; there was a systolic murmur at the apex and also a basal systolic murmur. The aortic second sound was accentuated, graded 2. Peripheral sclerosis was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 200 to 230 and a diastolic range of 95 to 135 mm. mercury.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 3, there was no sugar, erythrocytes were graded 4 to 5, and pus was graded 1. *Blood:* Hemoglobin, 11.7 gm. per 100 cc.; erythrocytes, 4,360,000; leukocytes, 6900; urea. 30 mg.; creatinin, 1.6 mg.; serum sulphates, 3.7 mg. The return of phenolsulphonephthalein was 30 per cent. The dilution test showed a minimum specific gravity of 1.008 and the concentration test a maximum of 1.016. A serologic test of the blood for syphilis gave negative results. An electrocardiogram revealed left ventricular preponderance and inversion of the *T* wave in Lead I and II.

Histologic study of the arterioles in a small piece of pectoralis major muscle removed for biopsy revealed definite and striking abnormalities. Numerous arterioles were seen in the sections, ranging from 25 to 200 micra in diameter. Marked thickening of the walls of the arterioles was noted in all those observed in the section, the average ratio of wall to lumen being 1 to 0.9. This ratio was quite constant, although a few arterioles had very little lumen. The arterioles were tortuous and there was a definite increase in the number and size of the nuclei of both intima and media. In one arteriole there was an organized thrombus almost entirely occluding the lumen and apparently compressing the wall. Cystoscopic examination disclosed right renal hematuria. There was marked deformity of the right pelvis with pyelectasis, the nature of which was indeterminate. The possibility of a postoperative polycystic kidney with pyelectasis and possibly ruptured cyst was not excluded.

A diagnosis was made of hypertension of Group 3, arteriolosclerosis, secondary anemia, myocardial degeneration and right renal hematuria. Whole blood was given intramuscularly daily for 3 days. Following this procedure the gross hematuria disappeared. On dismissal the patient was advised to follow a diet of 50 gm. protein, 2500 calories without extra salt, and fluids to the amount of 2000 cc. daily. Prescriptions were given for phenobarbital, grain ½ 3 times a day, theobromin and sodium bicarbonate, grains 5 each 3 times a day, and for ferric citrate, grains 15 3 times a day.

We learned that this patient died February 7, 1932.

On the basis of the evidence of actual arteriolosclerosis, the retinitis was considered to be due to primary hypertensive disease. It seemed likely that this retinitis would not heal completely, but would gradually become the chronic obliterative arteriolosclerotic type. The appearance of the arterioles in the biopsy of muscle was typical of that seen in many cases of severe progressive hypertensive disease in the active phase, uniform, striking reduction in

the ratio of the wall to the lumen and definite increase in the number and size of nuclei of the intima and media. It is of interest to note that there was thrombosis of an arteriole in both retina and pectoralis major muscle. These thromboses may be due to prolonged vasospasm, but it seems more reasonable to suppose they are secondary to the definite organic arterial changes. The clinical impression also was that the primary condition could be attributed to diffuse arterial disease with hypertension. The hematuria was evidently distinctly local. It was not deemed advisable to investigate this any further because of the condition of the patient.

Case 5.—A woman, aged 24 years, was admitted to the clinic October 13, 1930, complaining of headaches and amenorrhea. Headaches had commenced in October, 1928. They involved the vertex and sometimes the occipital region and occurred usually in the morning. A short time previous to admission the headaches had become more severe and of longer duration. One year previous to admission the systolic blood pressure was 150. During the 6 months previous to admission she had urinated 3 times nightly. Amenorrhea had been present for 2 years preceding admission to the clinic.

The skin was dry. Vision of the right eye was 6/10, and of the left eye, 6/7. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed acute retinitis similar to that seen in cases of subacute glomerulonephritis. Some of the retinal arterioles showed a suggestion of spasm, but definite generalized angiospasm was not demonstrable. Mild peripapillary edema, greater in the left eye, and a few cottonwool patches and hemorrhagic areas were present. Pus was expressed from the tonsils. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 11 cm. to the left; the second aortic sound was accentuated, graded 1. Slight peripheral sclerosis was present. The blood pressure studied over a period of 24 hours showed a systolic range of 150 to 190 and a diastolic range of 80 to 145 mm. mercury. Purpuric-like lesions of the skin were noted over the legs and feet.

Laboratory Tests. The specific gravity of the urine was 1.016, albumin was graded 2, there was no sugar, and there were a few erythrocytes observed on one occasion. *Blood:* Hemoglobin, 15.4 gm. per 100 cc.; erythrocytes, 4,480,000; leukocytes, 5700; urea, 26 mg. per 100 cc. of blood; the return of phenolsulphonephthalein was 45 per cent. In the dilution test the minimum specific gravity was 1.001 and in the concentration test the maximum was 1.035. A serologic test of the blood for syphilis gave negative results. The basal metabolic rate was −13 and −4. The electrocardiogram showed left ventricular preponderance.

The arterioles in a piece of pectoralis major muscle removed for biopsy showed an average ratio of wall to lumen of 1 to 1.6. This change was slight but quite constant. The arterioles were moderately tortuous. The nuclei of the media and intima appeared large but were not increased in number. A diagnosis was made of severe essential hypertension, amenorrhea and infected tonsils. October 28, 1930, tonsillectomy was performed. At the time of dismissal the patient was advised to follow a diet of 50 gm. protein, 1500 calories without extra salt.

The patient returned to the clinic February 26, 1931, complaining that headaches had persisted. She was troubled somewhat with restlessness. The vision was 6/6 in each eye. The fundi showed the retinitis to be more definitely of the angiospastic type. The arterioles were generally constricted with some irregularity peripherally which was spastic rather than defin-

itely sclerotic. The disks were rather pale and mildly edematous with elevation of about 1 diopter. A few cottonwool patches and hemorrhagic areas were present in the retina. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 12 cm. to the left; the second aortic sound was accentuated, graded 2. Peripheral sclerosis was slight. The systolic blood pressure was 175 and diastolic 130 mm. mercury.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 2, there was no sugar and there were a few erythrocytes and pus cells. *Blood:* Hemoglobin, 18.2 gm. per 100 cc. of blood; erythrocytes, 4,000,000; platelets, 130,000; coagulation time, 4 minutes, and bleeding time 2½ minutes; urea, 24 mg. per 100 cc.; the return of phenolsulphonephthalein was 40 per cent.

A diagnosis was made of essential hypertension of severe benign type with vasospastic features. On dismissal the patient was advised to follow a diet similar to that previously suggested, and in addition was given theocalcin 0.5 gm. 3 times a day.

The patient was again admitted to the clinic August 12, 1931. Her headaches were as troublesome as previously. For a month preceding admission she had noticed slight blurring of vision in the left eye, and she complained also of slight dyspnea. For 10 months previous to admission she had been too weak to continue her work. Examination at this time showed that vision was 6/6 in the right eye and 6/30 in the left eye. The retinitis had assumed the characteristics typical of malignant hypertension. The arterioles were definitely constricted and irregular. While some of the irregularity was still spastic, definite hypertensive sclerosis, graded 2, was present. The disks were hyperemic and edematous, elevated 1 diopter in the right eye and 2 diopters in the left eye. Cottonwool patches and hemorrhagic areas were present in the retina and an incomplete macular star had formed in the left eye. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 10 cm. to the left; the sounds were of good quality, there was a slight systolic impurity at the aortic area, the second aortic sound was accentuated, graded 2, and the second pulmonic sound was accentuated, graded 1. Peripheral sclerosis was graded 1 to 2. The blood pressure was 210 systolic and 145 diastolic.

Laboratory Tests. The specific gravity of the urine was 1.010, albumin was graded 2 and there was no sugar. *Blood:* Hemoglobin, 15.7 gm. per 100 cc.; erythrocytes, 4,000,000; leukocytes, 7500; urea, 24 mg., creatinin, 1.3 mg. and sulphates, 3.9 mg. per 100 cc. The return of phenolsulphonephthalein was 45 per cent. The electrocardiogram showed left ventricular preponderance, diphasic *T* wave in Lead II and inverted *T* wave in Lead III.

A diagnosis was made of hypertension of Group 4 and arteriolosclerosis. Roentgen rays were applied over the thoracicolumbar sympathetic chains. On dismissal the patient was instructed to follow treatment similar to that previously advised.

We learned that this patient died March 25, 1932.

At the first examination the retinitis was very recent, rather mild and showed only mild, rather localized angiospasm. It was impossible to distinguish the retinal picture from that seen in cases of acute or subacute glomerulonephritis. The relatively small amount of change in the arterioles of the pectoralis major muscle also suggests that at this time only slight organic changes had taken place in the general arteriolar bed. However, subsequent examinations revealed progression of the retinitis associated with the

development of generalized angiospasm and definite arteriolosclerosis, which placed it readily in the group associated with primary hypertensive disease. The possibility of primary glomerulonephritis was considered at the first admission to the clinic, as well as that of primary severe essential hypertension. Renal function was adequate, however, and there was no anemia. The presence of marked hypertension with so few other findings was atypical for glomerulonephritis. On the second admission the hypertension with its vasospastic features was predominant. It was not until the third visit, however, that the severe nature of the hypertension was appreciated.

Case 6.—A man, aged 25 years, was admitted to the clinic February 2, 1932, complaining of attacks of severe pain in the epigastrium and in the right upper quadrant of the abdomen, of 3 years' duration, and of dizziness and weakness. The abdominal pain was intermittent, lasting half an hour to 2 days and was not related to meals. It usually troubled him for about 3 days, recurred every 3 months, and was accompanied by anorexia, nausea and vomiting. In December, 1931, he had had his severest attack of pain, with vomiting of old blood, syncope and tarry stools, and an icteric tint to the skin. The icterus persisted for a month. At the time of admission he complained of a slight amount of pain, and of weakness and dizziness. For 2 weeks preceding admission he had had severe frontal headaches. For 2 weeks in December, 1931, the vision of the right eye was impaired. It gradually improved, however, almost to normal. For 3 weeks preceding admission, there had been some impairment of vision of the left eye. Marked dyspnea on exertion had followed the last attack of pain. He had been on a diet consisting largely of milk and eggs, but obtained little relief from the symptoms. For the last 2 months he had urinated once or twice a night. Transient pains in the arms and legs had been present for 6 weeks preceding admission.

Vision of the right eye was 6/7 and of the left eye, 6/30. The pupils, reflexes, and peripheral fields of vision were normal. Ophthalmoscopic examination revealed active angiospastic retinitis in each eye, with some evidences of commencing resolution. The optic disks were relatively anemic and their nasal margins were mildly edematous with elevation of 1 diopter. Hemorrhagic areas, cottonwool patches, and a few punctate spots of residual edema were present in the retina of both eyes. Localized areas of edema and pigment proliferation were visible in the choroid. The arterioles of the retina were generally constricted and markedly irregular, with evidences of active sclerosis, graded 3. A recent thrombus was seen in a small inferior arteriole of the left eye. A small temporal arteriole of the right eye was occluded apparently by an organized thrombus. The tonsils were hypertrophied. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 13 cm. to the left; there was a faint systolic murmur at the aortic area, and the second sound was accentuated, graded 2. Peripheral sclerosis was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 190 to 220 and a diastolic range of 100 to 145. Tenderness was present in the left portion of the epigastrium and under the right costal margin.

Laboratory Tests. The specific gravity of the urine was 1.018, albumin was graded 3, and there was no sugar. *Blood:* Hemoglobin, 11.1 gm. per 100 cc.; erythrocytes, 4,140,000; leukocytes, 8600; urea, 38 mg., sulphates, 5.5 mg. per 100 cc. A serologic test of the blood for syphilis gave negative results. The response after a test meal was normal. An electrocardiogram showed left ventricular preponderance and inversion of the *T* wave in all derivations. A roentgenogram of the thorax was negative except for slight

cardiac enlargement. Roentgenograms of the gall bladder and stomach were negative. A diagnosis was made of malignant hypertension and secondary anemia.

During the period of observation in hospital the patient had an attack of epigastric pain radiating substernally, associated with slight dyspnea. Two weeks after the first examination, the general appearance of the retinitis was the same, but the thrombus in the small arteriole in the left eye was undergoing organization and collateral circulation was being formed through the dilatation of a number of fine capillaries. The presence of an active lesion of the intima in the arterioles of the retina in this case favored the diagnosis of primary hypertensive disease. It was impossible to say at this stage whether the disease would develop into progressive hypertension (Group 4), or whether compensation might occur. The possibility of compensation with the development of relatively inactive arteriolosclerosis was suggested by the rapid development of collateral capillary circulation. The etiology of the abdominal pain was undetermined. It is possible that it was due to the vascular disease. It is of interest that the history which could be attributed directly to the hypertension was extremely short.

Comment. All these patients were rather young (24 to 38 years). Five had a fairly short history. Four of the 6 patients gave headache as a prominent symptom. Visual impairment was also noted by the same number. Four had mild secondary anemia which was of questionable significance. The electrocardiogram showed evidence of serious involvement in 2 cases. In 2 of the 6 cases glomerulonephritis apparently was primary, and the condition in the remainder could best be classified as primary diffuse arterial disease with hypertension. Two patients gave a history of gross hematuria. In Case 2 it seemed definitely related to the renal disease. In Case 4 apparently the local renal involvement was undetermined, and was distinct from the hypertension. One patient (Case 2) gave a definite history of edema, undoubtedly related to the nephritis. Two patients gave a history of puffiness of the eyes which was of questionable significance. Four of the patients died within 17 months of the discovery of the angiospastic retinitis.

The part played by angiospasm in the causation of retinitis in cases of toxemia of pregnancy has been demonstrated by Haselhorst and Mylius, and confirmed by one of us (Wagener). Continuance of the angiospasm in these cases for a relatively short period can be shown to result in definite organic injury to the walls of the arterioles in the retina. There is strong evidence in a considerable number of cases that there is similar organic injury to the systemic arterioles throughout the body. The occurrence of a similar chain of events in hypertensive disease is strongly suggested by the appearance and course of the changes in the retina in the case reported by Koenigsberger and Bannick and in the group of cases

here described. The significance of angiospasm in the development and course of primary hypertensive disease and of glomerulonephritis is emphasized by the rapid progression of the disease in these cases.

Conclusions. 1. Acute diffuse angiospastic retinitis can occur in both glomerulonephritis and primary hypertensive disease.

2. The course of the retinitis and its associated arteriolar lesions will often indicate the degree of organic injury to the systemic arterioles.

3. The retinitis is of serious prognostic significance.

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STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA.

A REPORT OF THREE CASES WITH REMARKS UPON THE CLINICAL ASPECTS.

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COARCTATION of the aorta is a rather rare congenital anomaly in which there is a complete or partial occlusion of the lumen of the aorta, and which in the adult type, described here, occurs at or near the insertion of the ductus arteriosus Botalli into the aorta.

The pathologic anatomy and clinical features of coarctation of the aorta have been admirably presented by Abbott[1] in her classical work published in 1928, and by others.[2] Its pathologic physiology has been studied in the greatest detail by Blumgart and his associates.[3] The typical roentgenographic findings have been described by Rösler,[2] Railsback and Dock,[4] Fray[5] and Ernstene and Robins.[6]

FIG. 1.—A stereoroentgenogram of the chest (M. A. E.). (Slightly retouched.)

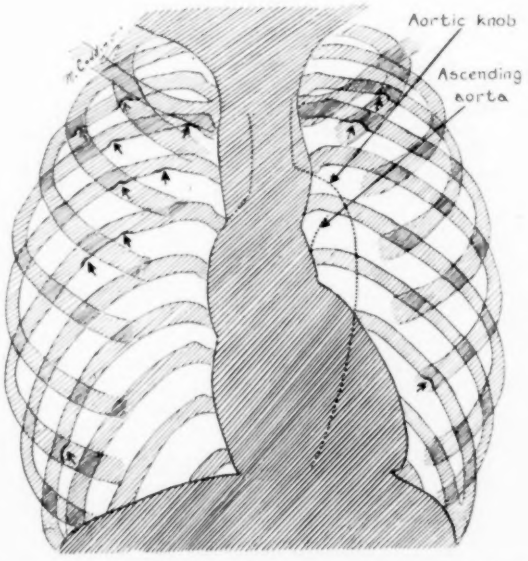

FIG. 2.—A diagrammatic sketch of Fig. 1, showing the roentgenologic signs of coarctation and in dotted lines, the aortic shadow in hypertensive heart disease.

Three typical cases have been observed at this hospital during the past 1½ years, during which time there have been 2845 admissions to the medical service. In each instance the signs were overlooked by more than one observer, and in 2 of the cases the diagnosis was first made by Roentgen ray. These cases are reported to reemphasize the clinical features which should enable one to make the diagnosis at the bedside and to comment on some interesting corollaries.

Case Reports. CASE 1.—H. B. M. (Med. No. 41118), aged 33 years, white, American intern, entered the hospital on May 20, 1932, for study. His life thus far had been entirely normal. In 1917, at the age of 18 years, he applied to a railroad company for employment but was not accepted because of a systolic murmur. Subsequently he volunteered for service in both the army and navy and was refused for the same reason. During the years 1917 to 1923 he led an extremely active physical life, spending the summers on a farm where he was able to carry on the most strenuous tasks without embarrassment.

In 1923 he entered college, where the routine physical examination again disclosed a systolic murmur, and for this reason he was not permitted to take part in vigorous athletics.

During 1927, his first year in medical school, he made 17 out of a possible 18 points in a Snyder circulation test. Throughout his medical school career he followed the custom of the medical students in devoting ½ hour in the afternoon to recreation in the form of squash, without any difficulty.

The systolic murmur and a moderately elevated blood pressure were consistently found at the routine physical examinations, but the diagnosis of coarctation of the aorta was not definitely established until November, 1930, when a roentgenogram was taken to ascertain if he had any unusual cardiac enlargement.

Physical examination revealed moderate suffusion of the facies, disproportionately greater development of the musculature of the trunk and upper extremities than that of the lower. The thorax was not unusual to inspection except for a vigorous suprasternal pulsation, more marked toward the right. There were no abnormal pulsations visible over the chest anteriorly or posteriorly. On palpation, however, definite arterial pulsations could be made out posteriorly on both sides over an area extending from the 2d to the 9th interspaces and from the spinous processes to the midaxillary line. In the interscapular area on both sides of the spinal column a harsh, blowing systolic murmur could be heard. It was loudest in the left interscapular area opposite the spine of the scapula. No pulsations could be felt over the chest anteriorly. The heart was not abnormal to percussion. The apex impulse could not be seen or felt. The supracardiac dullness measured 5 cm. in the 2d interspace. There was a harsh, rough, blowing precordial systolic murmur, best heard just over the xiphoid process. The radial pulses were equal, regular and synchronous at a rate of 66 per minute. The vessel walls were not thickened, beaded or tortuous. A definite pulsation could be felt in the popliteal and dorsalis pedis arteries. The pulsation of the abdominal aorta could not be felt while that of the femoral arteries was very feeble on the left side and barely perceptible on the right. The femoral pulse was detectably delayed in comparison with the radial pulse. Blood pressures in the recumbent posture were: right arm, 150/80; left arm, 154/90; right leg (popliteal), 122/94; left leg (popliteal), 120/90. By examination the lungs were entirely normal. The abdomen was not remarkable. There was no clubbing of the fingers. There

was a marked capillary pulsation in the fingers. No note was made of its presence or absence in the toes. No other congenital defects were found.

A roentgenographic examination on November 18, 1930, reported: A 7-foot film of the heart showed it was just inside the normal limits; the left ventricle was somewhat prominent and fluoroscopy showed a rather vigorous ventricular impulse. There was no other abnormality in contour, except that the descending aorta was not visible. The ribs showed marked indentation of the inferior borders quite similar to that seen in coarctation of the aorta. Measurements were Mr. 4.2, Ml. 10, G.V. 4.7, int. dia. 29.4 cm. A second examination on November 25, 1930, stated: Oblique views, both right and left, fail to show the aortic arch definitely. A.P. stereo on the Bucky diaphragm showed a definite flattening and a dimple in the 1st portion of the descending aorta just below the arch. There was widening of the supraortic shadow suggesting an increase in the size of the vessels. The vertebræ were apparently intact; the ribs showed the notching previously noted. Impression: Coaretation of the aorta. Electrocardiograms showed normal tracings.

The Wassermann and Hinton blood serum reactions were negative. Red and white blood cell counts were normal as was the urine examination. Skin temperature determined by the Tycos dermatherm showed the feet to be 0.7° cooler than the hands, whereas a similar simultaneous set of observations on a patient with a presumably normal circulation showed the feet to be 0.9° cooler than the hands.

Case 2.—M. A. E. (Med. No. 40260), aged 32 years, female, single, white, American, unemployed factory worker, entered the hospital for the first time on January 8, 1932, with the complaint of abdominal pain of 3 years' duration. Her family history and past history were irrelevant. She had been perfectly well until 3 years ago, when she first noted knifelike, griping pain in the left lower abdominal quadrant, present almost constantly ever since, aggravated by food, partially relieved at times by soda and defecation. It was occasionally accompanied by sour eructations and vomiting. Two years ago her persistent abdominal distress and menstrual disorders led to an appendectomy and subsequently a bilateral salpingectomy. It was at this time that she first noticed slight dyspnea on exertion and weakness of the legs on moderate activity. This weakness has steadily increased until at the present time she is unable to walk ½ block without experiencing a sensation of "knotty cramps" in the calves and a feeling that "her legs were going to double up beneath her."

Three months ago the abdominal symptoms again took her into another hospital where Roentgen ray examinations of the chest and gastrointestinal tract were reported as negative. The diagnosis at discharge was "neurasthenia, gastric." In January of this year she was referred to this hospital for study.

Physical examination revealed the following positive findings: the skin of the face and neck showed considerable vasomotor instability. The eyes were slightly prominent. The retinal arteries were normal. The thyroid was not palpable. There was a supernumerary nipple of the left breast but no other congenital anomalies. There was a forceful pulsation in the suprasternal notch. Carotid pulsations were accentuated on both sides of the neck. A blowing systolic bruit was heard in the supraclavicular area on the right. Pulsations could be seen in the interscapular area and felt from the 3d to the 9th intercostal spaces posteriorly on both sides. These pulsations were more marked on the left except in the region of the bellies of the latissimus dorsi muscles. In the interscapular areas a rough, blowing systolic murmur could be heard, the point of maximum intensity being over a small area, measuring 3 by 4 cm., just to the left of the 2d dorsal spine. By percussion the heart borders seemed slightly outside the

normal limits in size. Supracardiac dullness measured 6 cm. in the 2d interspace. At the apex auscultation revealed a soft, rumbling murmur early in systole which assumed a blowing character in late systole. This murmur was heard all over the precordium but best in the 3d left interspace. It was of less intensity than the murmur heard posteriorly. The radial pulses were equal, regular and synchronous; radial and brachial arteries were moderately thickened but not beaded or tortuous. The pulsations of the abdominal aorta could not be felt. Both femoral pulses were definitely palpable. The popliteal pulsations were not felt, but there were slight though definite pulsations over the dorsalis pedis arteries. Blood pressures in the recumbent posture were: right arm, 116/88; left arm, 135/90; right leg (popliteal), 102/88; left leg (popliteal), 100/88.

Stereoroentgenograms of the chest showed the lungs to be clear, except for a thickened septum around an azygos lobe at the right apex. The heart size was at the upper limits of normal, and showed a rather prominent first portion of the aorta which pulsated markedly under the fluoroscope. The aortic knob was less distinct than would be expected and there was an apparent depression in the border of the aortic shadow just below the knob. The vessels extending into the neck from the aorta were considerably enlarged. The ribs showed marked notching of the inferior borders with the smooth dense concavities characteristic of coarctation of the aorta.

A barium enema showed a normal colon. A gastrointestinal series was negative. Gastric analysis showed a normal free and total acid. Electrocardiograms showed left ventricular preponderance. The basal metabolic rate was +10. Urine, stool and blood examinations were not remarkable. The Wassermann and Hinton blood serum reactions were negative. Skin temperatures determined with the Tycos dermatherm showed the temperature of the feet to be 4° below that of the hands.

During the last week of her hospitalization and for the first 2½ months following discharge amidopyrin was found to be efficacious in relieving the abdominal distress, but she continued to have discomfort in her legs when ambulatory for ½ hour or more. During this period of time her brachial blood pressure was found to have risen to 152/120 in the left arm and 140/90 in the right arm. Pressures taken in the popliteal spaces remained essentially the same as those previously noted. When last seen, 4 months after discharge, she again complained of the previous abdominal pain, unrelieved by amidopyrin.

Case 3.—J. C. (Med. No. 40134), an Italian housewife, aged 28 years, entered the hospital on December 18, 1931, complaining of recurrent attacks of palpitation, dyspnea and pain of 7 years' duration. The family history was entirely irrelevant.

She was born in Italy and insofar as can be ascertained her childhood and youth were uneventful. There was nothing abnormal about the catamenia. *Eight years ago* (at 20 years) she had 2 severe attacks of epistaxis which required the attention of a physician. *Seven years ago* she was awakened quite suddenly out of a sound sleep by a pounding in her neck and knifelike, constricting precordial pain, accompanied by marked dyspnea and finally relieved by a hypodermic injection. For a week afterward she suffered from headache and intermittent attacks of constricting, knifelike precordial pain. Since then attacks of this nature have occurred at intervals of about 3 months and have been almost invariably initiated by profound emotional upsets. They were followed by several days of temporal headache, dizziness, scotomata scintillans and occasionally syncope. Five years ago, with the first of her 5 pregnancies, she had what she described as a "dream shock" when she was suddenly awakened out of a sound sleep by the symptoms enumerated above. This "dream shock" differed from her usual attacks in that she noted the following morning that

her right eye deviated outward and her face seemed to be drawn to the left. A similar episode occurred a year later with her second pregnancy. Both pregnancies terminated in miscarriage. In each of these instances 3 months passed before her eye "straightened" and her face assumed its normal contour. Three subsequent pregnancies were full-term deliveries and not accompanied by "dream shocks." During the past 7 months nocturia, orthopnea and edema of the ankles have appeared. Throughout this period there have been intermittent attacks of sharp pain in the flanks radiating to both lower quadrants, lasting only a few moments, disappearing spontaneously.

She was first seen in the out-door department of this hospital in October, 1931, where a physical examination revealed evidence of cardiac insufficiency and she was thought to have essential vascular hypertension and mitral stenosis. A roentgenogram of the chest, taken on November 30, 1931, revealed the typical signs of coarctation of the aorta and she was sent into the hospital for further study.

On *physical examination* her general appearance was not remarkable, except for moderately suffused facies and a warm skin, which was slightly flushed and moist. The pupils were equal and regular, and reacted promptly to light and on accommodation. The extraocular movements were normal. Ophthalmoscopic examination showed marked caliber changes of the retinal arteries, with moderate nicking at the arteriovenous crossings, but no exudate or hemorrhage. There was no evidence of facial palsy. The tongue protruded in the midline. The thyroid was not palpable. A loud systolic murmur was heard above the suprasternal notch, extending up into the vessels of the neck on each side to about the level of the hyoid bone, and in this region there was a marked arterial pulsation. The thorax appeared normal to inspection except for definite visible pulsations in the interscapular region synchronous with the systole of the heart. On careful palpation pulsations were felt in almost all the intercostal spaces posteriorly. Over all these vessels a loud, harsh, systolic murmur was heard, loudest in the interscapular area. The lungs were negative. The heart was enlarged both to the right and to the left. The action was regular and the sounds were of good quality. Over the precordium there was heard a harsh, systolic murmur which was transmitted to the vessels of the neck. The first sound was markedly reduplicated and the aortic second sound accentuated and snapping. At the base there was also a faint but definite systolic thrill. The radial pulses were equal, regular and synchronous. The vessel walls were slightly thickened but not tortuous or beaded. Femoral pulsations were felt with difficulty on the right side only. The popliteal, posterior tibial and dorsalis pedis arterial pulsations could not be felt in either leg. Pulsation of the abdominal aorta was not felt. Blood pressure determinations were: right arm, 300/125; left arm, 290/130; right leg, 135/100; left leg, 110/90. The blood pressures in the legs were taken in the femoral triangles, as they could not be obtained in the popliteal spaces. There was no clubbing of the fingers. There were no pathologic reflexes. There was slight pitting edema over the tibiæ.

A stereoroentgenogram of the chest showed definite cardiac enlargement to the right and left, with an apparent pleuropericardial adhesion on the right. The arch of the aorta was indistinct and there was a soft tissue shadow with the shadow extending upward on the left of the spine in the aortic area. The descending aorta was not visible. Several of the ribs showed small, smooth concavities on the inferior borders. A 7-foot heart plate showed it to be slightly above normal limits in size, with a rounded, blunt left ventricle. The previous findings of supraortic shadow on both sides and of erosions of the inferior margins of the ribs were confirmed. The heart measurements were Mr. 5.2, Ml. 8.2, G.V. 5, int. dia. 25.4 cm.

An A.P. stereo of the chest showed a definite notch in the lateral edge of the descending aorta just below the arch opposite the 5th thoracic vertebra. The basal metabolic rate on admission was +46, which in the course of 10 days of hospitalization came down to +8 without specific medication. Electrocardiographic tracings showed left ventricular preponderance. Clinical pathology was not remarkable. The Wassermann and Hinton blood serum reactions were negative. A urinary phthalein test showed 60 per cent excretion of the dye in 2 hours and 10 minutes by the intramuscular method.

Skin temperatures as determined by the Tycos dermatherm showed that the patient's hands and feet were essentially the same temperature, the latter being 0.4° warmer than the former, whereas in a normal control the feet were 1.2° warmer than the hands (in each instance the dorsi of the hands and of the feet were compared).

Since discharge from the hospital the patient has been seen at monthly intervals in the out-door department, and has continued to suffer from the same symptoms as on admission, but to less marked degree.

Comment. In considering these 3 cases from the point of view of diagnosis, we find that they have certain points in common with those reported by other observers, particularly in recent years.

First in the history one discovers that there were no symptoms referable to the cardiovascular system throughout childhood and youth. One of them, H.B.M., had never suffered any circulatory embarrassment. The second, M.A.E., had symptoms only since the age of 30 years, notably intermittent claudication, slight dyspnea and abdominal pain of a vague character. The third, J.C., developed symptoms of hypertensive cardiopathy at the age of 21 years.

The salient point to be drawn from these cases is the fact that evidence of hypertension or hypertensive disease in a young adult without renal disease should suggest the possibility of coarctation of the aorta before considering the case as one of idiopathic hypertension.

A less important, though none the less striking, feature is intermittent claudication of the legs in the same period of life. These symptoms in the second case were undoubtedly due to an inadequate circulation to the lower extremities and the coincident occurrence of abdominal symptoms may permit the inference that the cause of them could be on a similar basis. Her repeated abdominal operations without relief lend weight to this impression.

While the history may suggest coarctation of the aorta, there are certain physical characteristics of these cases that are pathognomonic of the condition. The presence of these should enable one to make the diagnosis. These signs are:

1. A harsh, blowing systolic murmur heard in the interscapular area just to the left of the spine and less intensely over the precordium.

2. Palpable and occasionally visible arterial pulsations over the posterior aspect of the thorax.

3. The blood pressure in the brachial artery is higher than that of the femoral (a reversal of the normal condition).

4. Normal or bounding arterial pulsations in the upper extremities with absent or feeble pulsations in the lower extremities.

5. Absence of a palpable pulsation in the abdominal aorta in the presence of a forceful systolic thrust in the suprasternal notch and vessels of the neck.

Equally striking are the roentgenographic findings, illustrated by Figs. 1 and 2:

1. Bilateral scalloping of the inferior borders of the ribs.

2. A blunt left ventricular shadow without the prominent aortic knob usually associated with hypertension.

3. A widened supraortic shadow.

4. Depression or dimpling of the left border of the descending aorta just below the point where the aortic knob is normally seen.

Laboratory studies and electrographic tracings do not contribute to the diagnosis. As would be anticipated, there is no remarkable contrast between the skin temperatures of the upper and lower extremities.

It is interesting to note that 2 of our cases were thought to have hyperthyroidism because of the presence of flushed facies, warm, moist skin, emotional instability, hyperactive heart, precordial systolic murmurs with a pulsation and bruit in the region of the thyroid gland.

With the diagnosis established, one can make predictions with reasonable accuracy in regard to the prognosis and probable cause of death.

The prognosis should be guided by symptoms and signs referable to circulatory failure and symptoms of hypertensive disease. These criteria are illustrated by our cases. H. M., who is asymptomatic, has a normal heart size by physical examination and Roentgen ray, and no left ventricular preponderance by electrocardiograph, has an apparently adequate collateral circulation as judged by the absence of symptoms, and only a moderate brachial hypertension. His outlook is certainly the best. M. E., who has slight dyspnea, intermittent claudication and an enlarged heart by physical examination (though a 7-foot film showed no enlargement), left ventricular preponderance by electrocardiograph, less easily palpable vessels in the legs, a degree of brachial hypertension similar to that of H. M., has probably a less favorable prognosis. J. C., on the contrary, with her marked symptoms of hypertensive cardiopathy, cardiac enlargement by physical examination and Roentgen ray, marked brachial hypertension and imperceptible pulses in the lower extremities certainly has a gloomy prognosis.

The probable mode of death as given by Abbott[1] in a series of 200 autopsied cases in the order of frequency is: (1) Cardiac failure; (2) rupture of the aorta; (3) cerebral accidents; (4) subacute bac-

terial endocarditis. Of her cases 74 per cent died before the age of 40 years, with an almost equal distribution (total 69 per cent) in the 2d and 4th decades.

Summary. Three typical cases of coarctation of the aorta are presented and discussed briefly with emphasis on the history and physical findings.

ADDENDUM.—During the first week in November, 1932, two more cases of Coarctation of the Aorta have been called to our attention. These cases were diagnosed in the Out-Door Department on purely clinical grounds without recourse to roentgenograms except for confirmation.

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A SIMPLE TEST FOR CAPILLARY RESISTANCE: THE "FLICKING" TEST.*

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ALTHOUGH petechiæ and vibices were observed by Hippocrates, it was not until 1556 that their presence was dissociated from pestilential fevers by Amatus Lusitanus,[1] who called the condition "morbus pulicaris absque febre" (flealike disease without fever). At times great difficulty was experienced in differentiating between an individual with purpuric manifestations and one infested with fleas. Following flea bites, petechiæ and at times ecchymoses and hematomas developed. In 1657 La Rivière,[2] to whom we owe the first complete description of purpura, mentioned petechiæ. Sir John Pringle,[3] in the 18th century, noted their presence in the arms

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of patients with jail or hospital fever after a tourniquet had been applied for venesection.

The first test for capillary resistance was devised by Koch[4] in 1890. This consisted of multiple intradermal punctures with a needle, after which, in certain cases, petechiæ appeared. It is significant that Koch described his test as of special value in purpura. A few years later Hecht[5] devised a simple instrument to test the resistance of the skin capillaries by the application of negative pressure. It consisted of a 3-way tube with a stopcock in the position leading to a small metal syringe; to the other tubes a glass cup and a mercury column were connected. With this method Hecht could create a negative pressure in the cup when applied against the skin and read the amount of pressure on the mercury column. In 1929 Silva-Mello[6] designed a more elaborate instrument which he called the "capillarresistometer" based on Hecht's invention. Schultz[7] discovered that striking the skin of the tibia or sternum resulted in the appearance of petechiæ. In 1911 Weill[8] brought out the tourniquet test ("signe du lacet") and demonstrated the appearance of petechiæ below the tourniquet. In the same year Rumpel and Leede[9] (German), Rocco and Frugoni[10] (Italian) and in 1914 Hess[11] (American) described similar tests. Rumpel and Leede studied this test in connection with scarlet fever and Hess with scurvy. Frugoni and Weill described the test as associated with purpura. Longo[12] claims that Hess, in 1913, demonstrated the appearance of hematomata in purpuric patients after subcutaneous injections of physiologic salt solution, but no record of such a test was found in the literature.

In our studies we have found the capillary resistance test to be positive in a large percentage of supposedly normal individuals. We have noted that certain factors, such as time of the year, diet, infection and constitution, affect the incidence of positive results. These data will appear in another article. The flicking test was suggested by one of us (H. W. J.) because while percussing the heart directly in 1 of our patients with purpura the organ was outlined by petechiæ. The test is performed as follows:

The tourniquet is applied 2 to 3 inches above the elbow for 5 minutes as for the capillary resistance test. After 4 minutes, by flicking the middle finger (Fig. 1) against the distended vein 3 or 4 times petechiæ appear. A control may be performed above the tourniquet by flicking with similar force, with a resultant erythema, but in most instances no petechiæ appear (Fig. 2).

At the suggestion of Dr. Krumbhaar,[13] the flicking was performed over an area between the veins. The result was positive, although not as marked as when the vein was flicked (Fig. 2*b*).

In cases with active purpura it may not be necessary to apply a tourniquet. Flicking may produce petechiæ in almost any part of the body.

The flicking test was performed in 108 normal individuals on whom the capillary resistance test was performed. A comparison brought out the following points: Of the 108 individuals, 55 had

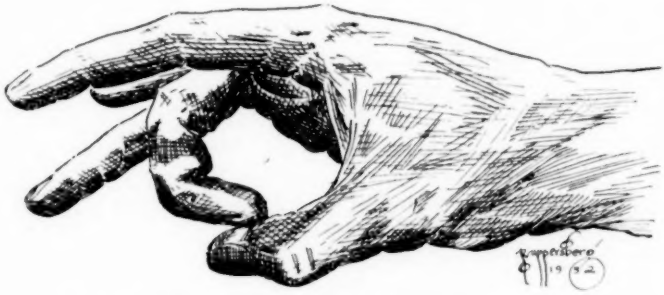

FIG. 1.—Position of the fingers for the performance of the test.

FIG. 2.—Appearance of the arm after performance of the "flicking" test: *a*, over a vein; *b*, in area without large veins.

both negative capillary resistance and flicking tests; 33 had a negative capillary resistance test and also a positive flicking test. In each instance of a positive capillary resistance test there was also a positive flicking test. On the other hand, not all cases in which the flicking test was positive showed a positive capillary resistance test. The total in this group having positive flicking tests was 53 (49 per cent) of the normal group.

It is of interest to note that there was an equal frequency of positive flicking tests in those that gave a personal or family history of hemorrhagic disposition, as well as those whose family or personal history was negative. Of 30 individuals who gave a history of frequent nosebleed, 18 showed a positive flicking test, whereas only 13 had a positive capillary resistance test. Of 7 who stated that they bruised easily, 4 gave a positive flicking test, while only 2 had a positive capillary resistance test.

The flicking test often is positive when the capillary resistance test is negative. It is 100 per cent positive in those cases in which the capillary resistance test (tourniquet test) is positive. It is, therefore, more sensitive than the capillary resistance test. In every case of acute purpura that has come under our observation the flicking test has been positive. During the convalescent period we utilize the capillary resistance as an indication of the condition of the capillaries. At times hemorrhagic phenomena are present even though the tourniquet test is negative. The flicking test in these cases remained strongly positive.

Summary. 1. The first mention of petechiæ in relation to a condition resembling purpura hemorrhagica was made by Amatus Lusitanus in 1556.

2. The first test for capillary resistance was devised by Koch, in 1890, and consisted of intradermal punctures with a needle.

3. In 1911 Weill brought out the tourniquet test. In the same year Rumpel and Leede, Rocco and Frugoni, and Hess, in 1914, described similar tests.

4. A new test, the flicking test, is described. The advantages are that it is easy to perform, yields more positives than the capillary resistance test (tourniquet test) and is positive after the capillary resistance test is negative.

5. In every patient with acute purpura hemorrhagica the flicking test was positive. In some of these cases the tourniquet test was negative.

6. In the study of a series of normal individuals the flicking test was found to be positive more often than the tourniquet test.

7. The positive flicking test indicates that the capillaries or venules rupture or become more permeable, resulting in the appearance of petechiæ. About 49 per cent of supposedly normal individuals show this phenomenon in the spring of the year.

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STUDIES OF ANEMIA IN PREGNANCY.

III. THE ETIOLOGIC RELATIONSHIP OF GASTRIC SECRETORY DEFECTS AND DIETARY DEFICIENCY TO THE HYPOCHROMIC AND MACROCYTIC (PERNICIOUS) ANEMIAS OF PREGNANCY AND THE TREATMENT OF THESE CONDITIONS.*†

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THE occurrence of moderate grades of anemia during pregnancy has long been considered physiologically normal. In the preceding papers of this series,[1,2] evidence obtained from the study of a group of normal pregnant women was presented which indicated

* A preliminary report of these studies was presented before the American Society for Clinical Investigation at Atlantic City, N. J., May 2, 1932.

† The expenses of this investigation were defrayed in part by the E. K. Lilly gift to the Harvard Medical School.

that true reduction in the *total* amount of hemoglobin in the maternal body (excluding the transient effect of hydremia) is found only in association with dietary deficiency or altered gastrointestinal function. Normal women in whom neither of these factors was present did not, in our observations, become anemic in pregnancy.

That severe and even fatal anemias may occur in pregnancy from no obvious cause has been known for a long time. In 1842 Channing,[3] of Boston, reported a series of such cases and, although a number of these were probably primarily cases of puerperal sepsis, others were undoubtedly cases of uncomplicated anemia of pregnancy. Bibliographic reference to the voluminous literature on this subject has already been made.[2] It is obvious that pregnancy may occur during the course of anemia due to any number of known causes, and it is likewise true that hemorrhage or infection complicating pregnancy, parturition or the puerperium may produce as severe an anemia as may similar events in nonpregnant individuals. In particular, puerperal sepsis due to hemolytic streptococci or other organisms may be accompanied by rapidly progressive anemia associated with blood destruction. It has, however, been shown[2] that pregnancy need not aggravate the degree of preëxisting anemia. It has also been shown that *under controlled conditions* spontaneous recovery following parturition apparently does not occur in the anemias of pregnancy.

In this communication will be presented observations concerned with etiologic and therapeutic factors made upon 36 consecutive cases of severe anemia of pregnancy with less than 45 per cent (7 gm. per 100 cc.) hemoglobin, or less than 2,500,000 erythrocytes per c.mm., due to none of the usual obvious causes of anemia. These observations, made upon cases of marked anemia, confirm the conclusions previously drawn from the study of normal pregnant women and suggest that these anemias are due either to a lack of specific substances of the diet necessary for blood formation or to an abnormality of the gastrointestinal tract preventing the proper utilization of such specific substances or to a combination of these two factors, in the presence of an increased demand to supply the fetal blood requirements. The condition of 3 of these patients has previously been described in detail.[4] The clinical histories and physical examinations of the 33 new cases so closely approximate those already given that they are not recorded here. The chief presenting symptoms were pallor, appearing usually about midpregnancy or later, a lack of sense of wellbeing and excessive fatiguability. In the more severe cases edema, dyspnea and prostration were observed. Splenomegaly, disappearing with adequate treatment of the anemia, was observed 4 times and fever without demonstrable infection, similarly abating, was observed 6 times. The latter occurred only in the patients with macrocytic anemia. The seriousness of these anemias of pregnancy was manifested by the

TABLE 1.—ETIOLOGIC FACTORS AND RESPONSES TO THERAPY OF 36 PATIENTS WITH SEVERE ANEMIA OF PREGNANCY.

TABLE 1.—ETIOLOGIC FACTORS AND RESPONSES TO THERAPY OF 36 PATIENTS WITH SEVERE ANEMIA OF PREGNANCY.

Case No.	Age (years.)	No. of births.	Type anemia.	State of gastric juice.	Diet.	Initial blood level.		After iron therapy.		Duration of therapy (days).	Control period.		Response during control period.
						Hgb. per cent.	R. B. C. (mils.)	Hgb. per cent.	R. B. C. (mils.)		Type.	Duration (days).	
1	34	13	Hypochromic	Achlorhydria	Good	33	2.87	81	4.60	38	..	..	.. *
2	25	2	Hypochromic	Achlorhydria	Poor	33	2.45	65	4.38	25	..	..	.. *
3	24	2	Hypochromic	Achlorhydria	Good	35	3.53	78	4.81	42	..	..	.. *‡
4	26	3	Hypochromic	Achlorhydria	Poor	42	4.83	87	7.34	95	No therapy	62	None
5	39	2	Hypochromic	Achlorhydria	Good	28	2.59	90	5.69	56	No therapy	10	None
6	39	6	Hypochromic	Achlorhydria	Good	31	2.16	98	6.61	70	No therapy	20	None
7	28	1	Hypochromic	Achlorhydria	Poor	36	3.33	91	5.16	47	No therapy	10	None
8	34	7	Hypochromic	Achlorhydria	Good	37	3.64	..	..	..	..	..	..†
9	22	4	Hypochromic	Achlorhydria	Good	41	3.30	..	..	..	..	..	..†
10	33	8	Hypochromic	Achlorhydria	Good	43	3.33	85	3.92	45	..	..	..‡
11	37	3	Hypochromic	Achlorhydria	Good	34	3.19	70	5.09	52	No therapy	180	None
12	32	7	Hypochromic	Achlorhydria	Poor	27	2.36	..	..	..	No therapy	180	None †
13	32	7	Hypochromic	Achlorhydria	Poor	29	3.44	75	4.60	180	No therapy	150	None
14	36	5	Hypochromic	Achlorhydria	Poor	35	3.22	74	4.92	66	No therapy	60	None
15	34	1	Hypochromic	Achlorhydria	Poor	34	2.87	65	4.09	35	No therapy	16	None
16	34	8	Hypochromic	Achlorhydria	Poor	38	3.29	80	4.95	55	..	..	..‡
17	26	4	Hypochromic	Achlorhydria	Poor	32	3.31	72	4.73	72	No therapy	17	None ‡
18	31	6	Hypochromic	Hypochlorhydria	Poor	27	2.12	..	..	..	..	..	..†
19	41	15	Hypochromic	Hypochlorhydria	Poor	44	3.96	70	4.18	86	..	..	..
20	29	5	Hypochromic	Hypochlorhydria	Poor	25	3.56	83	4.93	66	No therapy	43	None
21	21	1	Hypochromic	Hypochlorhydria	Poor	43	3.20	76	4.18	38	Liver extract	18	None
22	40	4	Hypochromic	Hypochlorhydria	Poor	40	3.87	80	4.71	75	Liver extract	10	None
23	32	7	Hypochromic	Hypochlorhydria	Poor	39	4.73	93	6.39	62	No therapy	98	None
24	39	8	Hypochromic	Hypochlorhydria	Poor	33	3.03	88	5.26	50	Liver extract	18	None
25	35	9	Hypochromic	Hypochlorhydria	Poor	44	4.42	70	4.54	100	No therapy	100	None
26	28	2	Hypochromic	Hypochlorhydria	Poor	41	4.04	..	..	..	No therapy	37	None †
27	27	3	Hypochromic	Hypochlorhydria	Good	30	3.24	90	4.96	96	No therapy	6	None ‡
28	37	8	Hypochromic	Normal acidity	Poor	43	3.83	..	..	..	..	..	..†
29	30	7	Hypochromic	Normal acidity	Poor	43	4.23	83	5.33	80	No therapy	12	None ‡
30	39	11	Hypochromic	Not examined	Poor	36	2.84	..	..	..	..	..	..†
31	30	4	Macrocytic	Achlorhydria	Poor	50	1.87	§	§	§	No therapy	52	..
32	34	7	Macrocytic	Achlorhydria	Good	45	1.98	80	3.87	37	No therapy	21	..
33	18	1	Macrocytic	Normal acidity	Poor	57	2.50	84	3.80	37	No therapy	12	..
34	32	6	Macrocytic	Hypochlorhydria	Poor	37	1.64	**	**	**	..	..	..‡
35	44	7	Macrocytic	Hypochlorhydria	Poor	20	1.05	**	**	**	..	..	..
36	39	10	Macrocytic	Hypochlorhydria	Poor	27	1.35	**	**	**	..	..	..

* Patient previously reported, reference (4). † Patient not treated. ‡ Patient treated during the course of pregnancy.
§ Liver extract No. 343, derived from 400 gm. liver, given. Final Hgb. 82 per cent, R. B. C. 4.09 million. ** See text for details of treatment.

fact that 4 patients developed severe complications, from which 2 died.

The 36 patients considered in this study were selected only after a critical search had eliminated the possibility of blood loss, infection or other complications being present. Detailed histories of the patients' diets over a period of years, as well as during pregnancy, were taken. The state of the gastric secretions was evaluated by routine gastric analyses as previously described.[1,2] Blood examinations were made of the infants born to these patients whenever possible.

Results. *Blood Picture.* Morphologic study of the blood showed that 30 of the 36 patients had anemia of the hypochromic (chlorotic, microcytic) type, with marked reduction in hemoglobin and less marked reduction of erythrocytes (Table 1). Leukocytes were normal or increased, as were the blood platelets. No abnormalities of the differential white blood cell counts were noted except that the polymorphonuclear neutrophils were frequently increased when the total leukocyte count was elevated. Icteric indices were normal. The erythrocytes were small and deficient in hemoglobin when studied on stained smear. Moderate variation in size and shape was noted, but true microcytes or macrocytes were not observed, nor were oval or tailed forms seen. This was corroborated by the determination of the mean corpuscular volume and hemoglobin concentration[5] in a number of cases. The average of the erythrocyte count of these 30 patients when first observed was 3,359,000 cells per c.mm. (range, 2,120,000 to 4,830,000) and the average hemoglobin (Sahli), 35 per cent (range, 25 to 44 per cent) (100 per cent hemoglobin = 15.6 gm. per 100 cc. of blood). The blood picture of these 30 patients, then, corresponded in every detail to that of the blood as noted in the early descriptions of chlorosis and as recently described as simple achlorhydric anemia,[6] hypochromic anemia with achlorhydria,[7] idiopathic hypochromic anemia[8] and chlorotic anemia with achlorhydria.[9] Its features are those of an anemia mainly due to defective blood formation.

Six of the 36 patients had anemia of the macrocytic (hyperchromic, pernicious) type. In these women the numbers of erythrocytes were more markedly diminished than the amount of hemoglobin, with a resultant color index above 1 (Table 1). Blood platelets and leukocytes were normal or diminished in numbers. Icteric indices were either normal or slightly increased. On smear, the erythrocytes showed moderate variation in size and shape with macrocytes, microcytes and occasional oval and tailed forms. The cells appeared well filled with hemoglobin. Mean corpuscular volume determinations showed an increased cell size (105 to 130 cubic micra) but not so marked as is frequently seen in true pernicious anemia. In general, then, these patients had a blood picture simulating that seen in typical Addisonian pernicious anemia and

conforming in every respect to the description given of the pernicious anemia of pregnancy.[10,11,12,13] This condition differs from Addisonian pernicious anemia by virtue of its occurrence in association with pregnancy or the puerperium and the absence of relapse, although all specific therapy be omitted, following recovery. In common with pernicious anemia, the blood picture is suggestive of an anemia mainly due to defective blood formation. Furthermore, achylia gastrica is not found as uniformly as in Addisonian pernicious anemia, only 2 of the 6 women reported here having this condition. It is of interest that 1 of these 2 women had normal gastric acidity when reëxamined 2 years later. A subsequent pregnancy was not complicated by macrocytic anemia, although marked gastric hypoacidity occurred during the course of this pregnancy.

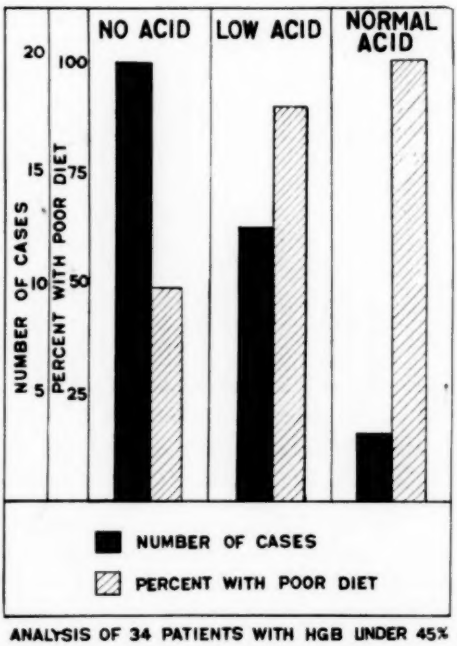

CHART I.—Gastric acidity and diet of 34 patients with severe anemia of pregnancy.

Gastric Analyses. The results of gastric analyses following histamin stimulation are graphically shown in Chart I. More than half of the total number, 19 patients, were unable to secrete free hydrochloric acid. A third more of the patients secreted little or no acid following alcohol test meals and subnormal amounts following the injection of histamin. Three patients only secreted a normal amount of hydrochloric acid. It is to be noted that the observations recorded in Table 1 and Chart I are postpartum. A

number of those patients who had low acidity after parturition had had complete anacidity during pregnancy. Four of the 6 patients with macrocytic anemia had free acid in the gastric contents and a fifth was found to have free acid 2 years later.

Over two-thirds of the patients of this series had definitely unsatisfactory diets during pregnancy and frequently prior to it (Table 1). Chart I, however, shows that half of the patients with anacidity had good diets, suggesting that achlorhydria alone or a state associated with it is capable of conditioning a deficiency of blood-building materials. The obvious and characteristic features of the poor diets were the low intake of iron and of proteins other than milk. The almost complete absence of meat proteins from the

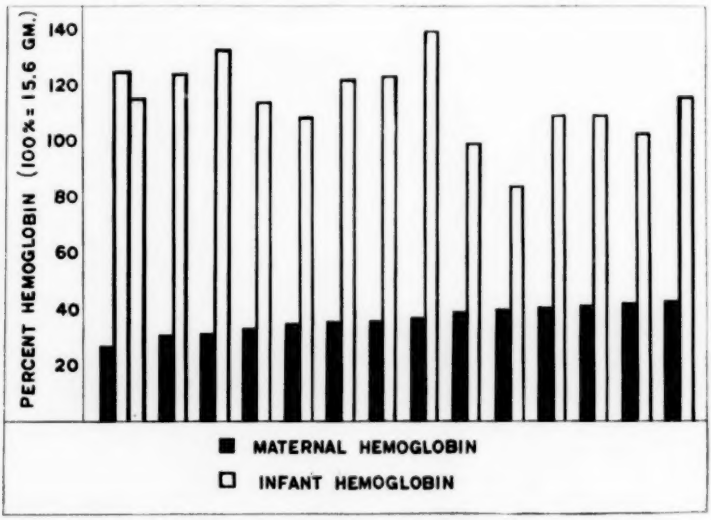

CHART II.—Comparison of infant and maternal hemoglobin in severe anemia of pregnancy.

diet was particularly noted in the patients with macrocytic anemia. No evidence of deficiency of fat, carbohydrate or total calories was observed in any of the diets. With the low protein intake of some of the patients there was probably also a low intake of vitamin B_2. A characteristic "poor" diet consisted of toast, butter, coffee, milk and sugar for breakfast; bread, butter, potato or rice, pastry or cake, tea, milk and sugar for dinner; and cereal, milk, bread and butter for supper; with fruit, meat and vegetables once or twice a week. The "good" diets included fruit, meat and vegetables 4 or more times a week, although many of the diets classified as good could not be considered optimal.

Blood Examinations of Infants. Examination was made of blood obtained from a freely bleeding puncture of the heel of 14 of the

infants born to the women who had been untreated during pregnancy. The results (Chart II) show that *no matter how anemic the mother, the infant is born with a normal amount of hemoglobin.* The blood of these infants was identical in every respect to the blood of a similar group of infants born of mothers not anemic. All infant blood examinations were made during the first few days after birth since there is normally a rapid decrease in hemoglobin and erythrocytes in the first weeks of life.[14]

These data, then, indicate that all of these patients had either a direct dietary deficiency or a disturbance of gastric secretion or, in many cases, a combination of both these factors. In addition, since the building materials used in the formation of the fetal blood are derived by necessity from the maternal organism, a condition analogous to chronic blood loss was uniformly present in all the patients.

Experimental Observations. In an endeavor to determine the exact nature of the deficiency and to correlate these observations with the two types of blood picture, various substances were administered, as in similar experiments previously performed in cases of idiopathic hypochromic anemia[15] and in Addisonian pernicious (macrocytic) anemia.[16,17,18,19,20]

Hypochromic Anemia. Control periods without therapy of from 6 days to 6 months were maintained in 16 of the 30 cases that had anemia of the hypochromic type. No significant reticulocyte responses or gains in hemoglobin or erythrocytes were observed. Three patients were given liver extract No. 343 (N. N. R.), derived from 600 gm. of liver daily. Small reticulocyte responses occurred in 2, but no significant gain in either hemoglobin or red blood cells was observed. Twenty-three patients, during or after pregnancy, were given 6 gm. of ferric ammonium citrate daily. In every case prompt reticulocyte responses and an average gain of 0.65 per cent (0.1 gm. per 100 cc.) hemoglobin per day occurred, together with rapid clinical improvement (Table 1, Chart III). In none of these cases was there any change made in the diet during the period of observation. However, in certain other patients, not included among the 30, diets rich in iron produced a slow remission of the anemia.

These observations suggest that the hypochromic anemia of pregnancy, like idiopathic hypochromic anemia, is due to a deficiency state correctable by iron therapy and either conditioned by abnormalities of the gastrointestinal tract or by a direct lack of iron in the diet. In addition, an analogy may be made between the blood requirements of the fetus and chronic blood loss associated with certain cases of idiopathic hypochromic anemia.

Macrocytic (Pernicious) Anemia. Of the 6 patients who had a blood picture practically indistinguishable from that of Addisonian pernicious anemia, the 2 with the least anemia were observed after parturition during control periods without therapy for 12 and 21 days, respectively, in which no improvement occurred. Imme-

diately thereafter, however, prompt reticulocyte responses appeared in each case, together with a gain of hemoglobin and erythrocytes following the daily administration of 6 gm. of ferric ammonium citrate. Clinical improvement, with a gain in appetite, likewise occurred so that these 2 patients, although receiving the same type of diet as before, began to eat much larger quantities of food, including meat. The data presented below suggest that this change in the diet of these 2 patients was of importance in the remission of the anemia. A third patient was given liver extract No. 343 (N. N. R.) derived from 400 gm. of liver daily. An exactly comparable clinical and hematologic response occurred as in the 2 cases mentioned above.

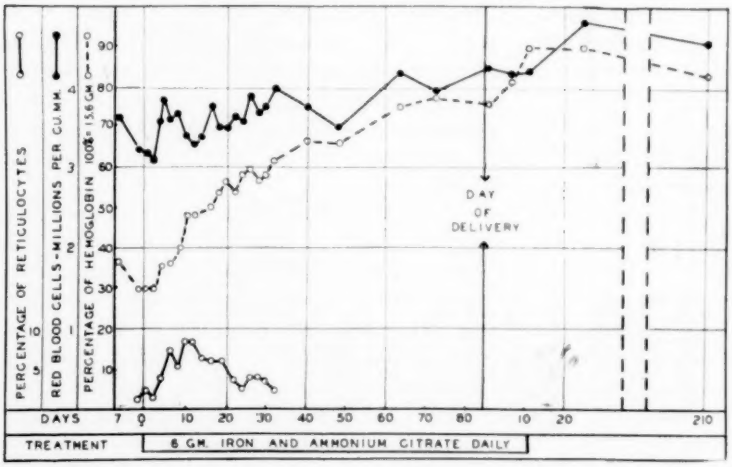

CHART III.—Typical response to iron therapy in hypochromic anemia of pregnancy.

These observations, together with the reports in the literature of the successful treatment of this macrocytic type anemia in pregnancy with liver extract alone, suggested the possibility that there might be a combined deficiency of iron and of the substance present in liver, as has been reported in pernicious anemia by Minot and Castle[21] and Beebe and Lewis.[22] To test this hypothesis a fourth patient was given first a small dose of liver extract potent for pernicious anemia which was followed by moderate reticulocyte response. Immediately thereafter iron was administered and produced a second reticulocyte response. During a third period without liver or liver extract the erythrocytes began to decrease. Daily doses of liver extract were then begun again and iron was continued. A third reticulocyte response, together with rapid clinical and hematologic improvement, occurred. It seemed probable, therefore, that an iron deficiency or a state improved by iron therapy brought about

by the same mechanism as in the hypochromic anemia of pregnancy was present at least in certain cases of the macrocytic type of anemia in addition to a deficiency of the type encountered in Addisonian pernicious anemia.

It has been stated[20] that any one or more of 3 mechanisms may produce the deficiency causing Addisonian pernicious anemia: (1) A lack of the specific intrinsic factor of the gastric juice, even with an adequate intake of extrinsic substrate found in beef muscle and yeast extracts; (2) a chronic lack of the substrate in the diet even with a normal amount of the intrinsic factor in the gastric juice; (3) a failure of the absorption or utilization of the product of the interaction of intrinsic and extrinsic factors. Accordingly, to determine if any of these mechanisms were involved in the pernicious

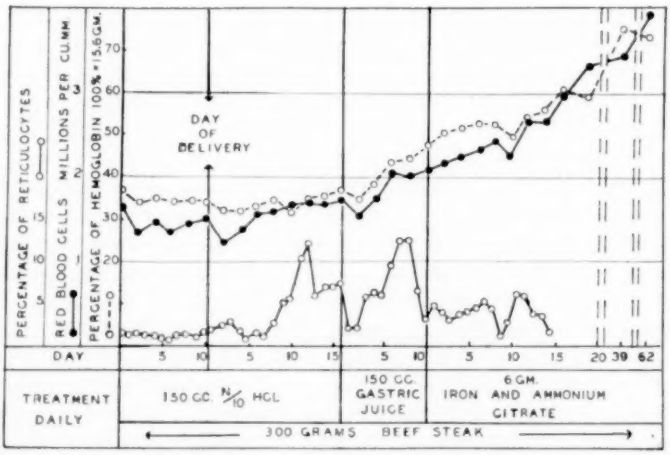

CHART IV.—Response to beef muscle, gastric juice and iron in macrocytic anemia of pregnancy.

anemia of pregnancy, a fifth patient, suffering from this type of anemia, first seen 10 days before delivery, was given successive periods of controlled therapy (Chart IV). First, this patient received daily for 10 days 300 gm. of beefsteak followed by 150 cc. $\frac{N}{10}$ hydrochloric acid. No hematologic response occurred. When, however, following delivery this same therapy was continued, a delayed but definite reticulocyte response occurred, together with a small gain in erythrocytes and hemoglobin in a period of 16 days.

This state of affairs suggests that before delivery the patient lacked the intrinsic factor of the gastric juice and that there was a partial return of the intrinsic factor in the gastric juice soon after delivery. When, next, in place of the hydrochloric acid, a like amount of normal human gastric juice was administered with the beef muscle there occurred a prompt second response of reticulocytes, together

with a gain of 0.5 million red blood cells in 10 days. This certainly suggests that the normal human gastric juice supplied something which had not previously been present in adequate amounts and which was not hydrochloric acid. Iron was then given, resulting in a small tertiary reticulocyte response and further improvement in her blood, suggesting in addition, as in the other cases of this type, a deficiency state which could be favorably affected by iron. It may be argued that the first reticulocyte response was in the nature of a "spontaneous" remission unrelated to the state of the gastric juice, despite the fact that in the control period of other cases without therapy after parturition, there was no evidence of remission. If this were the case, it is at least a remarkable coincidence that the second reticulocyte response was caused by the administration of intrinsic factor in the form of normal human gastric juice.

A sixth patient, first seen 18 days after parturition, was given 300 gm. of beefsteak daily followed at once by 150 cc. of $\frac{N}{10}$ hydrochloric acid for 10 days with no response of reticulocytes or mature red blood cells. Thereafter, 150 cc. of normal human gastric juice was substituted for the $\frac{N}{10}$ hydrochloric acid; this resulted in a small reticulocyte response. Iron was then administered in addition to the above therapy with a resultant second small reticulocyte response. At this point a transfusion of blood was given. Iron and beefsteak were continued, but gastric juice omitted. No response of reticulocytes or of mature erythrocytes followed. Gastric juice was resumed and a third small reticulocyte response occurred. Liver extract No. 343 (N. N. R.) was then administered, resulting in a reticulocyte response of 46 per cent at its peak, and rapid hematologic and clinical improvement. This case serves to illustrate the absence of any effect from transfusion of blood other than a temporary elevation of the red blood cells and hemoglobin, as well as the definitely positive effect of the mixture of beefsteak and normal gastric juice. The failure of the latter to give a more marked effect may best be explained on the basis that this mixture supplied a lesser amount of the necessary substance than did the dose of liver extract potent for pernicious anemia.

[In further confirmation of the above are observations made on 2 additional patients with macrocytic anemia of pregnancy who were studied since this manuscript was submitted. After control periods of 8 and 23 days respectively following delivery, during which no change occurred, each was given daily 16 gm. of autolyzed yeast (Vegex) rich in vitamin B_2. The first patient had a small reticulocyte response but no gain in erythrocytes during several weeks until normal gastric juice was administered with the autolyzed yeast, when a second and larger reticulocyte response occurred together with a prompt rise of erythrocytes. The second patient had a maximum reticulocyte response and rapid gain in erythrocytes under autolyzed yeast therapy alone. The first patient is entirely analogous to the fifth patient mentioned above, and the second patient illustrates that *after delivery, when these observations were made*, there was solely an extrinsic factor lack.]

These observations suggest that the macrocytic anemia of pregnancy, like other macrocytic anemias responding to liver extract, is due to a deficiency state brought about either by a direct lack of an extrinsic factor (vitamin B_2) in the diet or by a lack of an intrinsic factor of the gastric juice. In addition, a concomitant deficiency state corresponding to that observed in the hypochromic anemia of pregnancy is frequently present.

Discussion. The voluminous literature devoted to the consideration of anemia in pregnancy (see preceding paper[2]) emphasizes two possible etiologic factors: (1) A toxic substance elaborated by the product of conception which inhibits bone-marrow activity; (2) a hemolytic agent formed by the product of conception (usually stated to be a syncytial hemolysin) which destroys the maternal blood corpuscles. However, no evidence has been produced in proof of either of these theories, and the data presented in this and the preceding paper of this series do not support them, because comparable responses to therapy were obtained either during or after pregnancy and no responses occurred as a result of delivery alone.

In 1930[4] evidence drawn from 3 of the cases presented here was advanced in favor of the theory that the hypochromic anemia of pregnancy was due to a deficiency of blood-building materials brought about by gastric anacidity (or a defect associated with it), in the presence of fetal blood requirements. The data presented here, previously published in abstract,[24,25] indicate that in addition to such indirect deficiency "conditioned" by gastrointestinal defects, certain cases are due to a direct lack of blood-building materials in the diet, and others to a combination of direct dietary deficits and gastrointestinal defects.

The hypochromic anemia of pregnancy, then, is entirely analogous to idiopathic hypochromic anemia in that the etiologic mechanisms apparently responsible for its occurrence—direct dietary deficiency or indirect dietary deficiency conditioned by gastric anacidity and hypoacidity or a factor associated with these defects, and fetal blood requirement (which has the same effect as chronic blood loss in cases of idiopathic hypochromic anemia)—are apparently identical with the mechanisms operating in the production of idiopathic hypochromic anemia. Iron therapy is equally efficacious in the treatment of both conditions.

It may be thought that the number of observations made upon the macrocytic anemia of pregnancy is too limited to warrant discussion. However, the many similar experiments[16,17,18,19,20] performed upon patients with Addisonian pernicious anemia appear relevant to this problem and may serve as controls. That there is often a double deficiency present in this condition in pregnancy seems apparent, and it is known that this is not infrequently demon-

strable in pernicious anemia,[22,23] although usually only liver or liver extract need be given therapeutically. In Addisonian pernicious anemia there is ordinarily a permanent lack of the specific "intrinsic factor" from the gastric juice, which makes it necessary to supply the deficiency indefinitely. Cases have, of course, maintained normal blood conditions over long periods of time without liver or allied therapy, suggesting that occasionally there is a return of the specific gastric intrinsic factor, and, indeed, such a return has actually been demonstrated in 1 case of macrocytic anemia.[19] The observations reported here on the inefficacy of beefsteak alone during the progress of pregnancy suggest the lack of this specific gastric factor at that time. The moderate responses obtained with beefsteak alone following delivery suggest a return of this factor, although the more marked responses obtained when normal human gastric juice was administered in addition to the beefsteak, indicate that complete return had not yet occurred. That complete restoration does eventually take place is suggested by the fact that it has often been observed that these individuals do not relapse when once completely well following delivery.

The demonstration of the lack of intrinsic factor in these 2 cases of pernicious anemia of pregnancy must not be considered as evidence that this is true for all cases, since it is perfectly possible that, as has been suggested for Addisonian pernicious anemia,[19,20] cases may be discovered in which the lack of the extrinsic factor of the diet alone may be responsible for the anemia. Indeed, the cases reported by Wills[26] are probably due to this mechanism. The lack of correlation between the presence or absence of free hydrochloric acid in the gastric secretions and the presence or absence of the intrinsic factor need not be considered adverse to the hypothesis, since this lack of correlation has been demonstrated in Addisonian pernicious anemia.[19] That the acid alone is not involved is evidenced by the absence of response when acid was administered with the beefsteak.

These observations, then, indicate the analogous mechanisms involved in the production of the macrocytic anemia of pregnancy and Addisonian pernicious anemia, and indicate the efficacy of similar therapy in the two conditions. Likewise, similar mechanisms are indicated for the hypochromic anemia of pregnancy and idiopathic hypochromic anemia, and iron is found to be equally efficacious in alleviating either condition.

Conclusions. 1. The hypochromic anemia of pregnancy is due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of the fetal demand for blood-building materials, and may be completely relieved, either during or after pregnancy, by the administration of iron in large doses.

2. The macrocytic anemia of pregnancy is presumably due to a temporary lack in the gastric juice of the specific intrinsic factor which has been shown to be absent from the gastric juice of patients with Addisonian pernicious anemia in relapse. The ultimate complete return of this factor after delivery is hypothesized. It is believed that the lack of the extrinsic factor (vitamin B_2) from the diet may produce similar effects. The macrocytic anemia of pregnancy ordinarily may be completely relieved with liver extract, although iron is sometimes required in addition.

3. The similarity of the etiologic mechanisms involved in the hypochromic anemia of pregnancy and idiopathic hypochromic anemia, and in the macrocytic anemia of pregnancy and Addisonian pernicious anemia is pointed out.

4. Anemia in pregnancy does not cause any lowering of the infant hemoglobin or erythrocyte count at birth.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose coöperation this study was made possible. The technical work on the blood was chiefly performed by Miss Margaret Evans and Miss Charlotte Nicklin.

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AGRANULOCYTIC ANGINA (PERNICIOUS LEUKOPENIA).

A STUDY BASED ON 18 CASES WITH 9 NECROPSIES.

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THE concept of agranulocytic angina as a disease entity, rather than as a mere hematologic manifestation of various unrelated disorders, is still open to question. The opinion herein entertained is that agranulocytic angina exists as a valid clinicopathologic entity in the same sense that pernicious anemia is accepted as such. Not many years ago it was difficult to defend the nosologic purity of pernicious anemia. Today, with a practically specific therapeutic test for this disease in its relapse phases, one may confidently assert that a given individual has pernicious anemia even though there may be present an associated morbid process capable, in itself, of producing anemia.[1] In the light of this therapeutic test it is becoming apparent that certain conditions, which were formerly regarded as simulating pernicious anemia, may be actually contributing causes of the disease itself (sprue, fish tapeworm infestation, gastrointestinal carcinoma, etc.). It is now possible to exclude certain obscure pernicious-like anemias from the category of pernicious anemia by virtue of their failure to respond to adequate specific therapy. In a similar way, we believe, agranulocytic angina should be viewed as a disease entity which awaits the discovery of a specific therapy to stamp it with unmistakable validity.

The purpose of this report is to summarize the significant data of 18 cases of this disease studied in the hospital of the University of Pennsylvania since 1927. Prior to this date, our clinic failed to recognize the condition as such.[2] Of the 18 cases included in this report we have had personal contact with all but 2. Several (Cases 5,[2] 10[3] and 11[4]) have been previously reported by ourselves or others and 1 case (Case 8[5]) will be made the subject of a separate communication.

A summary of certain items of clinical importance is presented in Table 1. Cases 1 to 13, inclusive, are classical instances of

agranulocytic agina (pernicious leukopenia) about which no reasonable doubt can be raised. Cases 14 to 18 are, in our opinion, also examples of this disease, with certain atypical manifestations which are enumerated below.

TABLE 1.—SUMMARY OF CLINICAL DATA.

Case No.	Age.	Sex.	Race.	Previous attacks.	Duration of attacks.	Duration of remission.	Duration of life after onset.	Outcome.	Classification.
1 (Miss A.)	19	F	W	None	4 dys.	None	4 dys.	Dead	Acute
2 (Mr. J. C.)	78	M	W	None	3 wks.	None	3 wks.	Dead	Acute
3 (Mrs. C.)	68	F	W	Uncertain	Uncertain (chronic)	Uncertain	4 yrs.	Alive	Chr. contin.
4 (Mr. D.)	56	M	W	None	1 wk.	None	1 wk.	Dead	Acute
5 (Mrs. F.)	48	F	W	None	1 wk.	None	1 wk.	Dead	Acute
6 (Mrs. L.)	31	F	W	None	10 dys.	None	10 dys.	Dead	Acute
7 (Mr. W.)	68	M	W	None	5 dys.	None	5 dys.	Dead	Acute
8 (Mrs. S.)	42	F	W	Five	3–6 wks.	3 wks. to 18 mos.	2¼ yrs.	Alive	Chr. remit.
9 (Mr. E. S.)	22	M	W	None	5 dys.	None	5 dys.	Dead	Acute
10 (Miss S.)	26	F	W	None	2–3 wks.	3 yrs.	3 yrs.	Alive	Acute
11 (Mrs. L. S.)	58	F	W	Probably several	1–2 wks.	6–12 mos.	1 yr.	Dead	Acute*
12 (Mr. W.)	42	M	W	None(?)	2–3 wks.	None	2–3 wks.	Dead	Acute*
13 (Mr. M. W.)	52	M	W	None	3 days	None	3 dys.	Dead	Acute
14 (Mr. B.)	41	M	W	None(?)	(?)	Incompl.	2 yrs.	Dead	Chr. contin.?
15 (Mr. J. B.)	64	M	W	None	10 mos.	None	10 mos.	Dead	Chr. contin.
16 (Dr. R.)	42	M	W	None	5 mos.	Incompl.	5 mos.	Dead	Chr. contin.
17 (Mr. W. W.)	19	M	W	None	4½ mos.	None	4½ mos.	Dead	Chr. contin.
18 (Mr. K.)	54	M	W	Probably 5	1–2 wks.	2 wks. to 6 mos.	2 yrs.	Alive	Chr. remit.

* Uncertain history of prior attack.

CASE 14 (Mr. B.) had splenomegaly of sufficient magnitude to raise the question of "Banti's disease," Hodgkin's disease or of leukopenic leukemia. Against Banti's syndrome are the absence of demonstrable hepatic disturbances and the magnitude of the leukopenia (Table 2). Against leukemia and Hodgkin's disease are the absence of lymph node enlargements, and the presence of rectal and oropharyngeal lesions with profound granulocytopenia. This patient died with a terminal hemorrhage from the upper digestive tract, probably due to agranulocytic ulceration of the esophagus.

CASE 15 (Mr. B.) was complicated by the presence of carcinoma of the prostate with Roentgen ray evidence of possible spinal metastasis, but without other demonstrable bone marrow metastases at necropsy.

CASE 16 (Dr. R.) exhibited a moderate hyperchromic anemia (Table 2) which responded to massive liver therapy by a 10 per cent reticulocytosis and subsequent recovery from anemia. This response is suggestive of pernicious anemia, but the presence of free hydrochloric acid in the gastric analysis is against pernicious anemia. Furthermore, in spite of "erythron" recovery, this patient remained in a state of profound granulocytopenia, and his sluggish rectal ulcer never healed. These facts support the diagnosis of agranulocytic angina (rather than pernicious anemia, aplastic anemia, etc.). He died in another hospital, after 5 months illness, with a terminal leukocyte count of 450 per c.mm. (all lymphocytes) and a normal red cell and hemoglobin content.

CASE 17 (Mr. W.) is unusual in the fact that absolute mononucleosis was marked at the onset and again before death some months later. Careful hematologic examination during life and necropsy study of the spleen, liver and bone marrow altogether excluded monocytic and lymphatic leukemia as diagnostic possibilities. The case was otherwise a typical one

of agranulocytic angina with oropharyngeal and rectal lesions, and marked granulocytopenia.

CASE 18 (Mr. K.) is listed in the atypical group because we have not had opportunity of studying the patient during a relapse. His history and the leukocyte counts made during attacks and reported to us by the patient's wife (who is a physician) are practically diagnostic.

In the statistics which follow we shall include all of these cases as valid examples of agranulocytic angina. We have not included cases of acute benzene poisoning (1 seen with a terminal white blood count of 500 per c.mm., all lymphocytes), cases of acute arsphenamin poisoning with panmyelophthisic anemia, overwhelming septicemia with terminal leukopenia, cases of "idiopathic" aplastic anemia, cases of leukopenic leukemia and leukopenic Hodgkin's disease, cases of obscure anemia with leukopenia or cases of profound leukopenia from Roentgen ray.

The patient with the longest duration of life (Case 3) is in a chronic granulocytopenic status complicated by auricular fibrillation (now 4 years since onset). Case 10 has remained perfectly well, both clinically and hematologically, for 3 years since her violent attack.[3] Of the 11 cases (61 per cent) classified as acute only 1 is living (Case 10). The mortality in this "acute" group is over 90 per cent. Five cases (28 per cent) are classified as chronic continuous. Of these, 1 is alive (Case 3). Two cases are of the chronic remittent type (Cases 8 and 18). Both of these are alive and 1 of the latter is apparently cured (Case 8). Of the entire group of 18 cases, 14 are dead (78 per cent mortality), 2 are cured (in the sense that they have remained clinically and hematologically normal for 18 months and 3 years, respectively), and 2 are living but are either chronically granulocytopenic or are subject to frequent recurrent attacks of the disease.

The onset symptoms recorded in our cases are weakness and fatigue (100 per cent), malaise and feverishness (100 per cent), sore throat (79 per cent), sore mouth (47 per cent), cough (34 per cent), chills (34 per cent), vomiting (26 per cent), rectal distress (18 per cent), dysphagia (10 per cent). Significant physical findings are fever (100 per cent), oropharyngeal lesions (84 per cent), rectal or vaginal lesions (44 per cent), dental sepsis (44 per cent), slight cervical adenopathy (36 per cent), jaundice (18 per cent), moderate splenomegaly (18 per cent) (extending 1 inch or more below costal margin) and barely palpable spleens (10 per cent). A few petechiæ were noted in 1 of the patients, rectal ulcer bleeding in 2 and epistaxis in 1. This latter individual suffered a terminal hematemesis, presumably from esophageal ulceration. Although weakness and fatigue are most common symptoms, we have not been as impressed with their outstanding significance as have certain other observers.[6] We have seen patients with this disease (as well as patients with leukemia and other diseases) whose total

granulocytes have varied from zero to supernormal numbers without any other symptomatic or objective change of status.

TABLE 2.—LEUKOCYTES, RED CELLS, AND HEMOGLOBIN DURING ACUTE PHASE OF THE DISEASE.

Case No.	White blood cells.			Neutrophils.			Red blood cells.			Hemoglobin.			Classification.
	H.	L.	M.	H.	L.	M.	H.	L.	M.	H.	L.	M.	
1	500	200	300	0	0	0	4.5	4.5	4.5	90	90	90	Acute
2	2,100	1,200	1,500	16	0	6	3.9	3.1	3.7	65	57	60	Acute
3	7,500	1,100	2,000	18	0	9	3.6	3.2	3.4	74	43	60	Chr. contin.
4	1,200	500	800	0	0	0	4.4	3.3	4.0	85	60	70	Acute
5	600	500	500	0	0	0	4.4	4.4	4.4	82	82	82	Acute
6	1,000	800	900	0	0	0	4.8	4.6	4.7	98	90	95	Acute
7	1,250	50	600	0	0	0	4.6	4.6	4.6	85	85	85	Acute
8	4,000	250	1,800	14	0	8	5.0	4.5	4.8	98	87	94	Chr. remit.
9	1,200	500	1,000	0	0	0	4.0	4.0	4.0	70	70	70	Acute
10	3,400	600	1,500	8	0	6	4.8	3.2	4.0	98	62	80	Acute
11	1,000	200	600	0	0	0	4.8	4.3	4.6	98	90	95	Acute
12	6,500	900	1,300	83	26	30	5.2	4.5	5.0	98	83	90	Acute
13	500	500	500	0	0	0	3.5	3.5	3.5	80	80	80	Acute
14	3,800	700	1,300	34	0	20	4.5	3.7	4.0	88	72	80	Chr. contin.
15	3,200	1,900	2,400	16	0	5	4.5	2.6	3.5	95	51	80	Chr. contin.
16	3,200	450	1,500	40	0	20	4.3	2.5	3.8	85	68	75	Chr. contin.
17	16,300	1,500	2,000	33	0	55	4.6	2.4	3.5	90	37	65	Chr. contin.
18	2,500	1,600	2,000	?	?	?	5.0	5.0	5.0	100	100	100	Chr. remit.

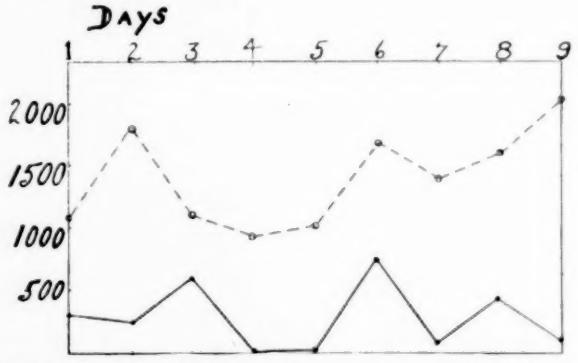
H = High. L = Low. M = Mean.

It is noteworthy (Table 2) that all but 2 patients exhibited complete absence of neutrophils at some stage of the disease. One of these 2 (Case 12) developed bronchopneumonia prior to the first blood count, and subsequently died of bronchopneumonia after hematologic remission had become established. In the other case (Case 18) data concerning the differential count during relapses are not available. The high total leukocyte count before death in Case 17 is unusual in that this represents an absolute increase in monocytes and lymphocytes (only 2 per cent of 16,300 white cells being neutrophils). We have no explanation for this, and none was found at necropsy, *i. e.*, no evidence of leukemia. The nearest approach to this granulocytopenic mononucleosis blood picture in our series is exhibited by Case 3, in whom only 18 per cent of 7500 white cells were neutrophils at one stage of the disease. Of the 18 cases, 13 showed leukopenia of less than 1000 cells. The lowest total leukocyte count (Case 7, 6 hours before death) was approximately 50 cells per c.mm. (personally enumerated and verified by us on two separate counts, each showing only 1 to 2 leukocytes in the entire ruled area of the counting chamber).

The mean red cell count and hemoglobin percentage (Sahli) in our series are 4,100,000 and 75 per cent, respectively. The only cases of red cell counts below 3,000,000 are in individuals with fairly obvious anemia-producing conditions: Case 15, with carcinoma of the prostate and bladder; Case 16, with bleeding hemorrhoids and fissure *in ano;* Case 17, with bleeding rectal ulcer. It is, perhaps, significant that the average of the lowest red cell counts

in the chronic cases is 3,000,000, and in the acute cases is 4,000,000, suggesting the importance of the time factor in the production of anemia in this disease. Although not included in Table 2, no significant pathologic variations in eosinophil, basophil and myelocyte cells were observed except their absence. During the few recovery phases we have never observed the myelocyte crisis recently described by Doan.[7] In the chronic continuous type we have been impressed by the observation that many of the few remaining neutrophils seen day after day in the blood spreads are nonfilament forms. We have been unable to adduce evidence of excessive peripheral leukocyte destruction, *i. e.*, no undue number of "smudge cells" or of excessive leukocyte fragility in this disease. Study of salivary leukocyte content in 3 cases yielded no consistent results except that in all instances the cells in the saliva were

CHART I.—RELATION OF WHITE BLOOD COUNT TO SALIVARY COUNT IN CASE 14.



——— Salivary count (white cells per c.mm.—all non-descript mononuclear cells.)

— — — White blood count (white cells per c.mm.—practically all lymphocytes.)

nondescript mononuclears with no definite polymorphonuclear neutrophils discernible. For example, in Case 17 salivary counts ranged between 15 and 500 cells per c.mm. during several successive days, while the white blood count was fairly constant at about 4000 cells per c.mm. In Case 13 salivary white counts ranged from 15,000 to 31,000 per c.mm. while the white blood count was 500 cells per c.mm. (all lymphocytes). This might suggest an inverse relationship (Isaacs), but opposed to such interpretation is our observation that an artificially induced leukocytosis (adrenalin) is associated with an increase in the salivary leukocytes. Furthermore, salivary leukocytes in a chronic case of the disease (Case 14) whose blood count was stabilized at 1000 to 2000 white blood cells per c.mm. during a week of observation ranged from 10 to 900 (Chart I).

TABLE 3.—MISCELLANEOUS LABORATORY DATA.

Case No.	Blood type.	Platelets (thou. per c.mm.).	Reticulocytes (per cent).	B.* and C. time.	C.R.†	Blood culture.	B.W.R.‡	Sed. rate.	Miscellaneous.
1	..	(Nor. smear)	1.0	...	..	Neg.			
2	A	...	...	...	..	Neg.			
3	..	180	...	...	..	Neg.			
4	O	281	0.2	...	..	Hem. strep.	Neg.		
5	..	...	...	...	..	Type III pneumo.			
6	O	112	...	...	..	Neg.			
7	..	...	...	...	..	Neg.	Neg.		
8	A	67 to 250	0.3	Nor.	Nor.	Neg.	Neg.		
9	B	294	0.1	...	..	Gram + coccus	Neg.		
10	O	107	0.1	...	..	Neg.	Neg.		
11	..	256	0.2	Nor.	Nor.	Neg.	Neg.		
12	A	151	...	Nor.	Sl. in 4 hrs.	...	Neg.	Nor.	
13	..	...	...	...	..	Nonhem. strep.			
14	..	52 to 150	1.3	Nor.	Nor.	...	...	Much incr.	Paul's heterophil antibody test neg.; D'Amato's hemoclastic crisis with 0.001 mg. old tuberculin neg. for tuberculosis.
15	..	200	...	...	..	Neg.	Neg.		
16	A	152 to 250	1 to 10	Nor.	Nor.	Neg.	Neg.	Mod. incr.	Paul's heterophil antibody test negative.
17	O	246	1.2	Nor.	Nor.	Hem. S. aureus	Neg.	Much incr.	
18	..	326	2.2	Nor.	Nor.	...	Neg.	..	Paul's heterophil antibody test negative.

* B. and C. time = Bleeding and clotting time.
† C.R. = Clot retraction.
‡ B.W.R. = Blood Wassermann reaction.

From Table 3 it is clear that marked thrombocytopenia is not common in this disease. Only 2 of our series exhibited less than 100,000 platelets per c.mm. (Cases 8 and 14). Other coagulation factors are normal. The finding of a normal sedimentation rate in Case 12 was so bizarre that the test was repeated and checked several times, with the same result. How a nearly moribund, highly febrile patient could exhibit a normal sedimentation rate has remained a mystery to us. His coagulation time, blood calcium and fibrinogen were all "normal." Further experiments are planned in this connection.

A review of our case histories* shows that the onset of the disease seemed to follow closely on the extraction of teeth in 4 instances (Cases 6, 10, 12 and 18). Eight of our patients gave no history of surgical or other trauma preceding the onset of angina (Cases 1, 2, 5, 7, 8, 11, 13 and 15). In 1 patient (Case 3) an acute gall bladder attack seems to have initiated the disease; in another (Case 9) an

* Owing to lack of space and because the essential data are presented in the tables the case histories have had to be omitted by the Editors.

intravenous injection of orthoiodoxy-benzoate and in another (Case 4) the surgical removal, under spinal anesthesia, of an old osteomyelitic sequestrum. Two of our patients had taken quinin intermittently during their lives (for supposed malaria). One was given diphtheria antitoxin, but the disease was probably already underway at this time. None of our patients presented any convincing evidence of allergic disturbance.

We have records of normal white blood counts and granulocyte percentages prior to the onset of the disease in 8 (Cases 3, 4, 6, 9, 10, 11, 12 and 15). In 2 of these cases we had previously observed a "normal" neutrophilic leukocytosis under appropriate conditions (*e. g.*, Case 10 exhibited a 20,000 white blood cell count with over 80 per cent "polys" after an emergency abdominal operation in 1927; Case 12 had 15,000 leukocytes with 78 per cent polymorphonuclears in 1929, the day after tonsillectomy). These facts make it difficult to uphold the hypothesis of a "constitutional predisposition" to this disease. In none of our cases was there any suggestion of an hereditary or familial or seasonal or contagious incidence of the disease.

TABLE 4.—TREATMENT.

Case No.	No. of transfusions.	No. of "stimulative" Roentgen ray treatments.	No. of grams pentose nucleotid (Jackson) injected.	Injections of purine bases.	"Reticulin" injections.	No. of vials liver extract ("343").	Liver extract (parenteral) injections.	Fixation abscess (turpentine).	Neoarsphenamin (intravenous) injections.	Removal of focal infection after onset of disease.	Formic acid injections (subcutaneous) (Dr. O. H. P. Pepper).	Outcome.
1	2	..	..	..	..	..	..	..	..	..	..	Dead
2	2	..	..	..	2	..	..	..	..	..	..	Dead
3	..	..	..	..	..	..	..	..	..	*	..	Alive
4	2	..	..	..	..	..	..	*	..	..	..	Dead
5	1	..	..	..	..	..	..	..	*	..	..	Dead
6	2	3	..	..	..	15	..	..	..	..	..	Dead
7	..	..	40	..	..	..	..	..	..	..	3	Dead
8	13	17	..	..	4	..	..	*	..	*	..	Alive
9	2	..	..	..	..	..	..	..	..	..	..	Dead
10	5	5	..	..	..	100	..	..	*	..	..	Alive
11	3	..	..	..	..	18	..	..	..	..	..	Dead
12	3	..	10	..	..	..	..	..	..	..	..	Dead
13	1	1	..	..	1	..	..	..	..	..	..	Dead
14	..	..	140	..	..	..	..	..	..	..	..	Dead
15	3	3	..	3	7	90	..	..	..	..	..	Dead
16	4	..	170	..	..	200	..	..	..	*	..	Dead
17	8	9	420	..	..	..	6	..	..	..	..	Dead
18	..	..	..	..	..	..	..	..	..	..	..	Alive

Additional treatment in all cases included oropharyngeal care, avoidance of drugs that might reasonably produce an anaphylactoid reaction (Dr. Pepper's suggestion), the use of orange juice, "vitavose," calcium gluconate, and cod-liver oil.

TABLE 5.—SIGNIFICANT NECROPSY FINDINGS.

Case No.	Digestive tract.	Genital tract.	Spleen.	Bone marrow.	Miscellaneous.
2 . . . . Mr. J. C.	Ulcers in mouth	Normal	170 gm.; many monos and lymphs, no polys	Sternum, ribs, and vertebræ show "congestion" and "no evidence of aplasia"	Myocardial degeneration; right upper lobar pneumonia; no polys in tissue sections.
4 . . . . (Mr. D.)	Ulceration and edema of uvula	Normal	250 gm.; acute splenic tumor; many mononuclear leukocytes; no polys	Sternum, ribs, and femur—intense congestion and hyperplasia of myeloid elements but no polys	Cardiac hypertrophy; pulmonary infarct.
5 . . . . (Mrs. F.)	Necrosis of tonsils and pharynx; edema and ulceration of larynx	Normal	Moderately enlarged; packed with red cells and mononuclear leukocytes; no polys	Marked red cell hyperplasia; "scarcity of myeloid cells" (femur only, and not examined by us)	In all organs, small necrotic patches without cellular reaction; widespread necrosis of walls of smaller arteries and veins.
6 . . . . (Mrs. L.)	Gingival ulceration; large hemorrhagic ulceration of descending colon	Large ulcer of vulva	270 gm.; acute splenic tumor; no polys	Femur and sternum marked myeloid and erythroblastic hyperplasia; no eosinophils or polys	Myocardial degeneration; congestion of lungs; congestion of adrenals and lymph nodes; no polys in sections.
11 . . . . (Mrs. L. S.)	Ulcers of mouth	Normal	140 gm.; congested with red cells; many lymphos and monos; no polys	Considerable myelocytic and myeloblastic hyperplasia in femur, tibia, and ribs; no eosinophils or polys	Nearly complete disappearance of lymphoid tissue throughout the body; heart's blood culture pure B. coli communis.
13 . . . . (Mr. M. W.)	Ulcers of gums and pharynx	Normal	240 gm.; acute splenic tumor; no polys	Moderate myeloblastic hyperplasia in islands in femur and tibia; other areas fatty	Myocardial and pulmonary congestion; moderate lymph node hyperplasia; acute interstitial focal nephritis.
15 . . . . (Mr. J. B.)	Normal	Prostatic Ca.	300 gm.; acute splenic tumor; a few polys	Exhaustion in femur; myeloid hyperplasia in ribs (myelocytes and myeloblasts but no polys)	Enlarged liver; recent lobular pneumonia.
16 . . . . (Dr. R.)	Ulcers of lip and gums with necrosis of alveolar process of right mandible	Normal	320 gm.; slight perisplenitis and marked chronic congestion; packed with red cells and mononuclear leukocytes; no polys	Sternum and ribs normal red; femur fatty (normal); sternum of practically normal cellularity (except for increased red cell congestion); many myeloblasts and normoblasts but no myelocytes or polys or eosinophils; a few megakaryocytes	Pulmonary infarction; terminal jaundice; liver considerably enlarged (cloudy swelling and fatty infiltration); a few slightly enlarged mediastinal lymph nodes showing inflammatory hyperplasia with many mononuclear leukocytes and macrophages and large lymphocytes but no polys.
17 . . . . (Mr. W. W.)	Ulcers in mouth and pharynx; perirectal inflammation; ulcer in rectum	Normal	250 gm.; overgrowth of large monos; no polys	Marked erythropoietic and myeloblastic hyperplasia in femur and tibia; arrest of maturity of myelocytes; no eosinophils or polys	No polys in tissues examined.

Treatment summary is presented in Table 4. Each of our patients, except 4 (Cases 3, 7, 14, 18) received 1 or more blood transfusions. The mortality in this transfusion group was 71 per cent. Pentose nucleotid (Jackson) was administered to 5 patients. One received 2 injections (20 gm. each) and died within 48 hours (Case 7). One received only 1 injection (Case 12), with an ensuing reaction of such alarming character that it was not repeated. This patient also died. Case 14 was given 1 intramuscular and 1 intravenous injection (10 gm. each) every day for 7 days, without any significant change in his chronic granulocytopenic status. He died a few weeks later. Case 16 showed a moderate increase in granulocytes the day after the first of 10 daily injections. This improvement seemed too soon to be attributed to nucleotid. The improvement was subsequently not maintained and a second complete course of this treatment was without effect. This patient reacted violently, with fever up to 104°, from each intramuscular injection, but tolerated the same dose (10 gm.) intravenously without any reaction. He died a few weeks after the last series of injections. Case 17 received 3 complete "courses" of nucleotid (10 gm. intramuscularly every day for 7 to 10 days and an extra dose intravenously on alternate days on 3 separate occasions) without any conclusive improvement in the granulocytopenic or clinical condition. This patient also died.

A summary of our experience with nucleotid is as follows: Two acute cases died before more than 1 or 2 injections had been administered; 3 chronic continuous cases were uninfluenced either hematologically or clinically by adequate dosage of the material and all are dead of the disease.

Summary and Conclusions.—1. The significant data of 18 cases of agranulocytic angina (pernicious leukopenia) are reported with 9 necropsies. All but 4 are dead (78 per cent mortality). Of these 4 only 2 can be considered cured.

2. The most promising treatment, aside from blood transfusion, seems to be pentose nucleotid (Jackson), although our experience with this substance has not been favorable. It seems more definitely to be useless in chronic cases of the disease.

3. Necropsy study has shown in more than half the cases thus examined by us a plentiful supply in the leukopoietic centers of the progenitors of the blood leukocytes. This virtual hyperplasia is in marked contrast to the profound peripheral leukopenia characteristic of the disease, and strengthens the previous suggestion[4] of an hypothesis of primary "maturation arrest," rather than primary "aplasia" to account for the hematologic phenomena of the disease.

4. Agranulocytic angina (pernicious leukopenia) seems to be a disease entity, although it is so closely simulated by certain other conditions that its nosologic status may remain debatable until a potent specific therapy is available, or some other pathognomonic feature is discovered.

NOTE.—For permission to report Cases 3, 6 and 15 we are indebted to Dr. T. Grier Miller and for Case 5 to Dr. Edward Rose. Our patient, Case 16, entered the Mount Sinai Hospital a few days before his death and we are indebted to Dr. S. L. Israel for his report of the clinical data covering this period and to Dr. R. N. Meranze, Director of Laboratories of the Mount Sinai Hospital of Philadelphia, for his excellent report of necropsy findings. We have had contact with 2 additional cases of this disease (both fatal) which we are not at liberty to include in this report. One of these also received adequate nucleotid therapy without ensuing benefit.

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DIAPHRAGMATIC HERNIA ASSOCIATED WITH SECONDARY ANEMIA.

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ALTHOUGH diaphragmatic hernia was formerly considered a rare condition,[1] the present popularity of Roentgen ray in gastrointestinal examination has resulted in this type of hernia being commonly demonstrated.[2,3,4,5] With more and more cases of diaphragmatic hernia diagnosed, it has been generally noted that some of the cases have an associated anemia.[6] So far as known, the English literature has not offered a collection of cases on this association, and it is therefore the purpose of this paper to present brief summaries on 22 previously published cases in the English literature and additional summaries on 6 unpublished cases.

Case Reports. CASE 1.—A man,[7] aged 43 years, complained that for a year he had suffered from exhaustion which occurred upon arising and was only relieved by prolonged resting. For several years he had had a sour stomach and, during the last few months, some epigastric pain which was relieved by soda. The appetite was fair and there had been only a few pounds loss of weight. The Roentgen ray showed a gastric ulcer of considerable size located on the lesser curvature of the pars media and a hernia of the cardiac portion of the stomach through the esophageal opening of the diaphragm. The stool on the meat-free diet was free from occult blood during our examination. There had never been a history of tarry stools, and to his knowledge occult blood had never been demonstrated in the movements. The blood showed a secondary anemia: hemoglobin, 42 per cent; red blood cells, 3,670,000; color index, 0.58; white blood cells, 7,850; neutrophils, 74 per cent; lymphocytes, 22 per cent; eosinophils, 4 per cent.

The degree of secondary anemia was unusual in our experience, particu-

larly in cases of gastric or duodenal ulcer, which have no history suggestive of bleeding and present no occult blood at the time of their examination. It is therefore interesting to note that all symptoms and Roentgen ray findings disappeared and the blood count became normal and remained so upon prescribing a modified Sippy ulcer régime.

CASE 2.—A woman,[8] aged 50 years, complained of frequent bilious attacks and vomiting for 15 years. Roentgen plates showed a large, diaphragmatic hernia containing one-half of the stomach. The blood showed: hemoglobin, 60 per cent; red blood cells, 4,100,000; color index, 0.73.

CASE 3.—A woman,[8] aged 51 years, was troubled with gas after eating and for the past several months had weakness, dizziness and palpitation. Stools showed occult blood. A gastrointestinal Roentgen ray study demonstrated a diaphragmatic hernia. The blood showed: hemoglobin, 55 per cent; red blood cells, 3,800,000. The patient was operated upon and no structural cause for the anemia was found, either at the site of the herniation or other sites along the intestinal tract. The hernia was not reduced and occult blood and anemia persisted.

CASE 4.—A woman,[8] aged 73 years, had tarry stools 4 years ago, and occult blood during the last 2 months. There was no indigestion, although the gastrointestinal Roentgen ray study demonstrated a diaphragmatic hernia. The blood showed: hemoglobin, 45 per cent; red blood cells, 2,500,000.

CASE 5.—A woman,[9] aged 59 years, was in an automobile accident 9 years ago following which she experienced epigastric pain. Recently she had vomited coffee ground material. Blood examination showed: hemoglobin, 75 per cent; red blood cells, 4,720,000. She was operated upon, and a diaphragmatic hernia containing a greater portion of the stomach was corrected. She was relieved of her trouble. Harrington believes this case was congenital in origin, as the automobile accident was trifling and there were vague digestive upsets prior to it. Bleeding was supposedly due to a demonstrable erosion of the stomach mucosa at the site of the hernia.

CASE 6.—A woman,[9] aged 60 years, had indigestion for 35 to 40 years. Blood was noted in the gastric contents. Blood study showed: hemoglobin, 68 per cent; red blood cells, 3,650,000. The Roentgen rays had demonstrated an extensive diaphragmatic hernia. The patient was operated upon with relief of symptoms.

CASE 7.—A woman,[9] aged 54 years, had suffered a marked kyphosis since 5 years of age due to a fall. Since that time she had always had heartburn and indigestion. Four years ago she had experienced a severe pain in the left side of the thorax. A physician had treated her for some time for anemia, and had noted blood in the stools. Blood examination showed: hemoglobin, 46 per cent; red blood cells, 3,700,000. Operation was performed and a thinning of the gastric wall at the site of angulation through the hernia was noted. The hernia was satisfactorily reduced and 4 months later the blood showed: hemoglobin, 95 per cent; red blood cells, 5,400,000.

CASE 8.—A boy,[9] aged 12 years, complained of vomiting for 9 years and hematemesis during the past year. Blood study showed: hemoglobin, 70 per cent; red blood cells, 4,500,000. Operation was performed disclosing all of the stomach and part of the transverse colon through the diaphragmatic hernia. Because of the bleeding, the patient had been treated for gastric ulcer.

CASE 9.—A woman,[9] aged 49 years, had epigastric pain and vomiting since childhood. Recently she had vomited blood several times. The Roentgen plates showed an ulcer at the point of angulation of the stomach through the hernia. At operation no ulcer was noted, although there was definite thinning of the gastric wall at this point.

CASE 10.—A woman,[9] aged 59 years, had attacks of epigastric pain associated with dyspnea for 12 years. Examination of the blood showed: hemoglobin, 58 per cent; red blood cells, 3,700,000. At operation the cardiac portion of the stomach was found through the hernia and a gastric ulcer high on the stomach near the cardia. It was thought that this was a congenital hernia with a true inflammatory ulcer.

CASE 11.—A man,[9] aged 35 years, suffered a severe fall 8 years ago and for the last 6 years had stomach trouble. His hemoglobin was 70 per cent and the red blood cells 4,520,000. Blood was present in the vomitus. Operation disclosed a greater part of the stomach through a hernia with shallow ulceration at the point of angulation.

CASE 12.—A young boy[9] had stomach trouble due to a diaphragmatic hernia. His hemoglobin was 20 per cent. There was no hematemesis or melena. Operation was decided upon and a phrenicotomy was done prior to an abdominal approach. With this measure only the gastric symptoms were relieved and the hemoglobin had risen to 68 per cent at the end of 3 months.

CASE 13.—A man,[10] aged 55 years, had suffered from lower sternal pain after eating. The gastrointestinal Roentgen ray study showed one-third of the stomach in the hernia, and an ulcer in that portion just beneath the diaphragm. On medical treatment the pain disappeared, and at the end of 6 weeks Roentgen rays failed to demonstrate an ulcer crater. One year later the symptoms returned with occult blood and occasional vomiting of dark-colored material. The Roentgen plates demonstrated a recurrence of the ulcer. Operation was performed and the patient died of shock.

CASE 14.—A man,[10] aged 58 years, had hematemesis in 1922. In 1927 he had pain in the lower left chest and in 1928 the stools showed occult blood with another attack of hematemesis. The hemoglobin dropped from 62 to 42 per cent. The Roentgen plates showed a diaphragmatic hernia with large gastric ulcer. The patient was operated upon, but died from the shock.

CASE 15.—A girl,[11] aged 19 years, was poorly developed, anemic, had dysmenorrhea and scattered chest pains. An operation was performed for a pelvic condition without relief. A second operation was performed some time later which showed a diaphragmatic hernia. This was corrected and the patient was relieved of all her trouble.

CASE 16.—A boy,[12] aged 7 years, had frequent vomiting spells. Blood study showed: hemoglobin, 65 per cent; red blood cells, 3,400,000. Operation was performed for correction of a diaphragmatic hernia and the patient was relieved.

CASE 17.—A woman,[13] aged 45 years, suffered from abdominal colic for 4 to 5 years which was produced by food and required morphin for relief. Blood study showed: hemoglobin, 64 per cent; red blood cells, 3,920,000. At operation three-fourths of the stomach was removed from the diaphragmatic hernial opening, and the patient was relieved.

CASE 18.—A man,[14] aged 42 years, had a left side pain 16 years ago while wrestling, and since then had recurring attacks of abdominal distress. No blood was noted in the gastric contents which showed normal acid, nor was there blood in the stools. "The blood gave a picture of secondary anemia of moderate grade." Fluoroscopic examination showed most of the stomach in a diaphragmatic pouch. A recent communication from one of the authors states that this patient has progressed on medical treatment, and "his blood picture is better than 10 years ago; he now has only a moderate grade of secondary anemia."

CASE 19.—A woman,[15] aged 65 years, suffered from epigastric distress for 10 years with sour eructations and infrequent vomiting. The blood count showed: hemoglobin, 45 per cent; red blood cells, 2,000,000. Roentgen rays demonstrated a diaphragmatic hernia.

CASE 20.—A woman,[16] aged 52 years, had epigastric distress after meals for 1½ years which was relieved by belching. The stools showed occult blood, but the gastric contents showed none and there was a hyperacidity. "She had a moderate secondary anemia." The gastrointestinal Roentgen ray series showed a duodenal ulcer and herniation of the stomach through the diaphragm. The hernia was reduced and a posterior gastroenterostomy was performed, with relief of symptoms. One and a half years later the hernia returned, but the patient remained asymptomatic and there was no recurrence of the anemia.

CASE 21.—A woman,[16] aged 51 years, had weakness of such severity during the past year as to force her to give up work. There was no digestive trouble with the exception of constipation. The blood study showed: hemoglobin, 50 per cent; red blood cells, 3,800,000. The stools repeatedly showed occult blood. She was operated upon and the stomach was examined for bleeding, but no source was discovered; neither was any malignancy noted. A diaphragmatic hernia was not touched and the anemia persisted so that 10 months later it was of such severity as to make the patient a chronic invalid. No other cause of this anemia has been ascertained.

CASE 22.—A boy,[17] aged 16 years, had vomited after excessive eating since the age of 18 months. The blood showed "a decided diminution in red corpuscles, and normal number of white cells with hemoglobin 70 per cent." An operation disclosed the pylorus, duodenum, some omentum and liver herniated into the right chest cavity.

CASE 23.—A boy,[18] aged 19 years, had epigastric pains after meals for 8 months. This was relieved by vomiting, but with no hematemesis. "On admission to Guy's Hospital the patient was very thin and anemic." The Roentgen rays showed a left diaphragmatic hernia which was operatively corrected. The surface of the stomach was inflamed and bruised near the pylorus from friction against the front and inner edge of the hernial opening.

CASE 24.—A boy,[19] aged 2½ years, had weakness and pallor since birth. His blood showed: hemoglobin, 20 per cent; red blood cells, 2,800,000. His condition was diagnosed as anemia of unknown origin, and responded well to iron. Later he died of bronchopneumonia, and it was found that almost the entire stomach and portion of the duodenum was through the right diaphragm. No mention was made of ulceration or bleeding points.

CASE 25.—A woman,[20] aged 45 years, had noted a burning epigastric pain for a few months, and which was relieved by alkalies. Four years ago she had similar trouble at which time bleeding into the intestinal tract was noted. Blood examination showed: hemoglobin, 35 per cent; red blood cells, 2,760,000. Gastrointestinal Roentgen ray series showed a right diaphragmatic hernia. The patient was transfused and then operated upon with correction of the hernia. No cause of bleeding was noted. One month later the hemoglobin was 67 per cent; however, a recent communication states that the hernia has returned and with it a recurrence of the anemia.

CASE 26.—A woman,[20] aged 41 years, had been pale for several years, and 3 years ago was successfully operated upon for hemorrhoids. One year ago the hemoglobin was 18 per cent, and a blood transfusion was given. Now she presented pain in the left upper quadrant which radiated to the shoulder blades, and the blood showed a hemoglobin of 40 per cent with red blood cells 2,500,000. The stool was negative for occult blood, and a normal amount of gastric acid free from blood was noted. Operation disclosed the cardiac portion of the stomach in a left diaphragmatic hernia, and no mention was made of a bleeding point. The patient expired from a postoperative bronchopneumonia.

CASE 27.—A woman,[21] aged 34 years, states that 1 year before she was very anemic, and now suffered from palpitation and dyspnea. For some

time she had gas and bloating after heavy meals. The blood showed: hemoglobin, 30 per cent; red blood cells, 3,580,000. The stools were positive for occult blood. An operation disclosed the stomach, a large loop of the transverse colon, and the first part of the small intestine in a right-sided diaphragmatic hernia. The hernia was satisfactorily reduced. The hemoglobin, 5 months later, was 65 per cent; 8 months later it was 72 per cent, with red blood cells, 4,000,000. This hernia was considered congenital and no bleeding point was made out.

CASE 28.—A woman,[22] aged 64 years, presented a diaphragmatic hernia under the Roentgen ray. Several members of her family had a similar condition. As long as remembered she had been anemic. A recent blood count gave hemoglobin 55 per cent and red blood cells 3,750,000. Other data were lacking.

Discussion. These cases have been selected because they illustrate cases of diaphragmatic hernia in which there was definite blood loss, an anemia, or both.

The literature is considered inaccurate in determining the dependence of anemia on the hernia, as many cases are presented from the Roentgen ray viewpoint, as well as from a medical or surgical angle, and the blood picture has not been closely considered. Those cases of traumatic diaphragmatic hernia followed by immediate gastrointestinal bleeding have not been included in the series. These are a problem for the traumatic surgeon.

In analyzing the above series 17 are females and 11 are males, making the anemia more common in the former. Age is a factor, as 19 cases occurred after the age of 40 years. Twenty-five cases are thought to be congenital; only 3 have a possible traumatic cause. This difference is probably due, as stated above, to the fact that traumatic cases with immediate bleeding have not been included.

As usual, in cases of diaphragmatic hernia, the gastrointestinal symptoms may be of such a mild nature that the patient does not ask for medical aid for many years. Twelve cases had symptoms of indigestion running from 6 to 35 and 40 years; 1 middle-aged patient had trouble since "childhood." Nine cases has trouble for a period of months only, and 7 cases did not mention any gastrointestinal complaints. When symptoms are noted, however, they are suggestive of any type of abdominal upset. Fourteen of the cases had demonstrable loss of blood; so that coupled with their complaints, the impression of a bleeding ulcer is given rather than of a diaphragmatic hernia.

The rôle of ulceration in causing anemia is most important. This ulceration may be a true peptic one, independent of the hernia as demonstrated in 5 cases, or a definite abnormality in the gastric mucosa as shown in 5 cases. In the true peptic ulcer group Case 13 illustrates a temporary relief of all trouble on a medical regimen directed toward the ulcer. With the reappearance of the ulcer crater 1 year later, and a return of symptoms and bleeding, the ulcer and not the hernia was responsible for his anemia. Case 1

also demonstrates that the ulcer is a most important factor, as ulcer treatment resulted in the blood count returning to normal. Case 20 is similar in that operative treatment was given for both the ulcer and the diaphragmatic hernia with relief. This relief continued even after the recurrence of the hernia. Case 10 responded to operative treatment directed toward both the ulcer and the hernia. It is felt that in Case 14 the large gastric ulcer was responsible for the anemia. These cases, therefore, indicate that the hernia was a coincidental finding, with anemia produced by bleeding from true peptic ulcers. The fact that more peptic ulcers are not noted with diaphragmatic hernia also indicates that the herniation does not necessarily predispose to peptic ulcers.

In contrast to these cases are those with an abnormal mucosa at the site of herniation. Cases 5, 9, 11 and 23 showed such definite changes when their mucosa was inspected at operation. Case 7 must also be included in this group, and is of special importance because a follow-up blood count was made after the operation. Before operation her count was hemoglobin 46 per cent with red blood cells 3,700,000 and 4 months later was red blood cells 5,400,000.

The most interesting and perplexing cases of all are those with anemia which present no apparent anatomic cause for bleeding, and whose only unusual finding is the diaphragmatic hernia. In Cases 6, 15, 16, 17, 22 and 26 it is merely stated that an operation for hernia correction was performed, and no other gastrointestinal lesion was noted. We are led to believe that these operations were successful and that the anemia was corrected, although no definite follow-up reports were given. Case 27 is one in which operation disclosed no bleeding point; yet, after correction of the hernia we are given definite figures to indicate that the hemoglobin rose from 30 to 72 per cent in 8 months. The hernia here probably caused the anemia. In Cases 3 and 21 no bleeding points were noted, the hernia was not reduced and the anemia persisted with no other apparent cause. Case 18, although not presenting apparent blood loss, did show an improvement on "medical treatment" in his secondary anemia. This anemia, however, still persists to a lessened degree. Case 25 indicates a decided relationship between the hernia and the anemia. An operation to correct the hernia was followed by a rise of hemoglobin from 35 to 67 per cent in 1 month; however, the hernia returned and so did the anemia.

Case 12 stands alone in that only a phrenicotomy was done and nothing else; yet the hemoglobin rose from 20 to 68 per cent in 3 months. We might suppose that paralysis of the diaphragm relieved considerable vascular tension in the gastric wall with no further oozing of blood.

Cases 2, 4, 8, 19, 24 and 28 merely report a diaphragmatic hernia with a secondary anemia present.

In all these cases there is only one type of anemia apparent, and

that is the secondary type. This is determined on the low color index, the lack of nervous changes, the absence of glossitis and the presence of free gastric acid when a test was made for it.

No work has been done to show just how the hernia can produce an anemia, though two possibilities present themselves. One is that there is some obscure change in the gastric mucosa which may result in a deficiency productive of an anemia. In this series only 4 cases have a definite mention that a bleeding point was not found when looked for at operation. All of these cases had a history or demonstration of blood loss. None of them had a histologic examination of the stomach mucosa, and none showed an achlorhydria when tested for. This series, therefore, does not contain sufficient evidence to assume there is a gastric deficiency productive of an anemia. The second possibility is that of blood oozing from the gastric mucosa due to venous congestion, caused by compression of the stomach by the diaphragmatic muscles; that is, the cause of the anemia would be a mechanical one. In those cases where there is no demonstrable bleeding point, one must always eliminate other sources of blood loss.

The treatment of these cases with anemia depends upon a most careful study to exclude frank ulceration. If this condition can be demonstrated the usual medical ulcer regimen such as diet and alkalies with secondary anemia therapy should be instituted. However, if this treatment does not relieve distressing symptoms or the anemia and there is no other demonstrable cause for the anemia an operation should be done. The ulcer should be considered as of the greatest importance in these circumstances. In cases in which only the hernia is present and no other cause for the anemia is apparent a try at the medical ulcer treatment is again worth while. If the symptoms of anemia are sufficiently distressing and the medical treatment is a failure, surgery should be instituted.

Summary. 1. Twenty-two previously published and 6 previously unpublished cases of diaphragmatic hernia with an associated anemia are briefly summarized.

2. Of these cases presented, sex, age, cause, duration of symptoms and character of symptoms are briefly discussed.

3. Of the 28 cases, the diaphragmatic hernia was a primary factor in producing anemia in 8 cases, true peptic ulcer was a complicating factor in 5 others. Insufficient data, postoperative death and the possibility of an anemia of unknown origin eliminated 3 other cases. The other 12 cases allow only the supposition that the anemia was caused by the hernia.

4. The anemia is secondary in type, being caused, it is thought, by venous oozing due to a compression of the stomach by the diaphragmatic muscles.

5. Treatment consists of the medical ulcer regimen, including diet and alkalinization, plus secondary anemia treatment. If this fails,

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5. Treatment consists of the medical ulcer regimen, including diet and alkalinization, plus secondary anemia treatment. If this fails,

and if the anemia is severe, surgical correction of the lesions present is worthy of consideration.

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PARENTERAL LIVER EXTRACT THERAPY IN THE TREATMENT OF PELLAGRA.

A PRELIMINARY REPORT.

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THERE is still a wide difference of opinion as to the exact etiology of pellagra although it is generally believed that a deficient diet plays the major rôle in its causation. Based on this belief the usual treatment consists, essentially, of a diet rich in vitamin G or Goldberger's P.P. factor. Underhill[1] thinks that a lack of vitamin G is not the sole factor, and that too much reliance should not be placed on this agent in the prophylaxis and treatment of the disease. He quotes Turner's view that vitamin G therapy has made a poor showing and that this is probably an argument against its specificity.

Mellanby[2] suggests a double deficiency as the cause, a lack of vitamin G being responsible for the skin lesions, and a lack of vitamin A being responsible for the cord lesions. Guthrie,[3] in a review of 336 cases, found a high incidence of achlorhydria and, like other observers suggests that there is possibly a relationship between pellagra and pernicious anemia. Cohn, Minot, *et al.*, from their study of pernicious anemia, were doubtful that the antipellagra vitamin was responsible for the effectiveness of liver in the treatment of that disease, but stated that further investigation was being done by them.

Wheeler and Sebrell[5] have tested 35 foodstuffs for their efficiency in the prophylaxis and treatment of pellagra, and one of these, liver, was found to be rich in vitamin G. Goldberger and Sebrell[6] found that liver extract, when fed to dogs on a basic diet, prevented and relieved black tongue and suggested that it might be a valuable temporary expedient in the treatment of pellagra. Boggs and Padgett[7] in a review of a series of 102 cases also stressed the value of *liver* in the diet (not liver extract).

At Parkland Hospital our most difficult problem in the treatment of pellagra has been the patient's coöperation in the dietary régime. Loss of appetite is a marked feature of the disease, and most patients refuse to eat sufficient food. Many of them refuse to take such foods as milk, fresh meats and green vegetables. Therein lies the probable reason for many observers reporting poor results in the treatment of the disease, thus discounting the efficiency of vitamin G therapy.

In view of this difficulty and, also, to try out the clinical value of liver extract in the treatment of pellagra, we decided to use the parenteral method of administration. Our treatment consisted of rest in bed and a general house diet without any additional vitamin G containing foods. Liver extract No. 343 was given in daily doses of 2 cc. intramuscularly without variation. The usual site of injection was the deltoid or gluteal region. Practically no inconvenience was experienced from the injections. No other medication of any kind was used.

Twenty-two cases were treated in this manner, 20 in the hospital and 2 outside. The results have been spectacular. The earliest change in the symptoms was a rapid return of the appetite. In every case, in from 3 to 7 days, the appetite became either normal or in many cases ravenous. In our experience this never occurred in the usual dietary treatment when the disease was active. Cowgill[8] has shown that dogs have an abrupt loss of appetite in from 3 to 5 days, when fed a diet free from undifferentiated vitamin B and that when the vitamin is restored the appetite returns in a few days.

The general clinical improvement was rapid in all cases. No deaths occurred in the series, which is also remarkable. The gastro-

intestinal, skin, mental and nervous symptoms improved much more rapidly and completely than with the dietary treatment in previous cases. The average time of hospitalization was much shorter than previously.

There was a moderate amount of anemia in all cases. In a few cases in which reticulocyte counts were made the response was not marked (the highest was 4.7 per cent). Achlorhydria was present in 81 per cent of the cases.

A brief summary of some of the most severe cases will illustrate the efficiency of the treatment.

Case Abstracts. Case 10.—Mrs H. B., white, aged 59 years, a farmer's wife, was admitted to the hospital on August 5, 1932, with intense burning of the forearms and lower legs, sore mouth and loss of appetite. There was no history of a previous attack; however, she stated that for the past year she had had frequent attacks of colic. Constipation had been present for many years. She was greatly depressed and unable to give a connected history.

Examination revealed: a white woman much older in appearance than the age would indicate. There was moderate emaciation. The skin was in fair condition and apparently normal except on the arms and legs. A very inflamed symmetrically distributed dermatitis of the bullous type covered both forearms from the wrists to and including the elbows, and both lower legs from the ankles to a short distance below the knees. The mucous membrane of the mouth was very inflamed. The tongue was thick and beefy looking, and along its margins there were several necrotic ulcers. The temperature was 104° F., the pulse 120, the red cell count 4,190,000, hemoglobin 80 per cent. The gastric contents showed no free hydrochloric acid.

Liver extract was started the day of admission. Five days later the appetite had greatly improved and the temperature was declining. The sore mouth had improved to such an extent that eating was not painful. No local treatment was used on the blistered areas. On the 7th day the patient was alert mentally, and requested that she be given more food. By the 13th day the temperature was normal and the dermatitis had disappeared leaving smooth, healed, pinkish-looking areas. On the 19th day the patient left the hospital free of all clinical evidence of pellagra.

Case 3.—Mrs. P., white, aged 52 years, a farmer's wife, was admitted to the surgical service on May 10, 1932, because of profuse bleeding from the rectum. No surgical condition was found and she was transferred to the medical service. For the past 20 years she had suffered from indigestion following each meal. Most of the time she had passed large quantities of gas. She had had 7 children and had had many spontaneous abortions. There had been intermittent pains in the epigastrium for 10 years, and for 6 years there had been an intermittent bleeding from the bowels. The latter had occurred frequently during the past year, and with every bowel movement for the past month. She had gradually lost weight for several years, amounting to a total of 50 pounds. For 3 years shortness of breath had been very distressing, at times requiring her to stop and rest before she could speak. Spells of vomiting were frequent and always followed a meal in which some article of food had disagreed with her. Her appetite had been poor for many years, and she had confined her diet largely to cereals because of the epigastric pain. There had been alternate constipation and diarrhea, but no history of any previous dermatitis.

Examination: the skin was very dry and rough over the entire body, and in many small areas there was marked desquamation. In each flank

there was an area 18 by 12 centimeters in which the skin was very rough and pigmented, giving it a dirty yellowish color. Above each heel across the tendo Achillis the skin was in large, rough, pigmented folds. The hands were rough, and especially across the knuckles, the skin was pigmented. The reflexes were moderately exaggerated, with slight general spasticity. The mental responses were slow. The basal metabolic rate was −3. Achlorhydria was present.

Liver extract was begun May 17, 1932 and on June 14, 1932 the patient was discharged clinically well. One month after leaving the hospital her weight had increased 40 pounds. There was no evidence of pellagra, all symptoms having completely disappeared. At this time this woman was doing her housework and also helping in the fields.

A report from this patient on January 24, 1933, indicates that the mental responses and body weight are normal. The skin on the forearms is slightly rough. The gastrointestinal tract is showing some disturbance, evidenced by occasional indefinite abdominal pains. However, she has drifted back to her old habit of restricting her diet. In all probability there will be a recurrence of the pellagra syndrome this summer.

Case 13.—Mrs. H., white, aged 42 years, a farmer's wife, was admitted to the hospital August 5, 1932. Three years previously while 7 months pregnant, she had an acute illness which was diagnosed influenza, but she delivered normally at term. Since that time she had gradually lost weight and strength. For the past 6 months she had been practically helpless due to weakness and stiffness. And for the past 2 months she had been confined to the bed.

Examination revealed a marked general spasticity with greatly increased reflexes. Walking was slow and unsteady. The face was expressionless. The tongue could not be protruded beyond the teeth and swallowing was difficult, the food regurgitating through the nose. The arms were strongly flexed at the elbows and the hands held across the chest with the thumbs down into the palms. The arms could be only partially extended by force, and this was painful. The speech was very slow and deliberate and almost unintelligible. A pregnancy of 4 months complicated the picture. The abdomen was greatly distended with gas. The skin was dry, and in each flank there was a large area in which the skin was rough and pigmented. The face, neck, and lower legs up to the knees presented a yellowish tanned appearance as if sun burned. The general picture was that of a Parkinsonian syndrome and pellagra.

The patient had daily injections of 2 cc. of liver extract, beginning August 12, 1932, and continuing until October 12, 1932, except for 1 week when they were discontinued inadvertently. Improvement was noticed after the first week and was continuous until the patient was discharged October 12, 1932. After 1 month of treatment the muscular spasticity had improved sufficiently for her to fold surgical dressings. At the present time, 1 month after leaving the hospital, the improvement is continuing, although no liver extract has been given except orally since her discharge. The facial expression is now nearly normal. No difficulty is experienced on swallowing. There is no rigidity of the neck muscles. The left arm shows some spasticity and is held in flexion, but can be straightened without pain. The appetite is normal. The gait is steady. The pregnancy is developing in an apparently normal manner. The tanned appearance of the skin has disappeared, except on the face. This patient is now doing her housework including the cooking for a family of 5.

Baker, Bradley and Longcope,[9] in a study of the effect of liver therapy on the neurological manifestations of pernicious anemia, found that improvement was noted in 59.9 per cent of the signs and

symptoms in 8 patients after more than 10 months' treatment. Continuous treatment of neurological manifestations of pellagra with liver extract may likewise cause more improvement than formerly as is evidenced in the above case.

CASE 6.—Viola W., mulatto, laundress, aged 28 years, married, was admitted to the hospital on July 7, 1932, complaining of extreme weakness and abdominal pain. For 3 months she had been feeling weak, lost her appetite, and her abdomen began to distend with gas. Her hands and feet began to get black 3 weeks before admission. One week later her mouth became sore, and sores appeared on her hands.

Examination: the most noticeable sign was a very marked emaciation, so extreme that she could not stand without holding to the bed. There was a slight general spasticity with the elbows and knees flexed. The knee jerks were greatly exaggerated. There were fine tremors of the fingers and tongue. Mentally the patient was slow. Depression was so marked that she did not notice what was going on about her. The abdomen was distended and extremely tender throughout. The mucous membrane of the mouth was fiery red. The tongue was thick, red, and had several small necrotic ulcerations. The skin across the backs of the hands, tops of the feet and lower abdomen was a sooty black. Across the knuckles of each hand was a thick black crust with multiple small bleeding points. Around the vagina there was an inflamed area about 2 inches wide which showed less pigmentation than the other areas. The temperature was 101° F., and the pulse rapid. The red cell count was 4,250,000, and hemoglobin 80 per cent, white cells 7600.

Liver extract was begun July 12, 1932, and 1 week later the crusts on the backs of the hands were easily peeled off with tissue forceps. The underlying skin was smooth and free from bleeding points. The temperature varied from 101° to 102° for the first week. For the next 2 weeks it was irregular and rose at times to 101°, after which it remained normal. The appetite was normal after 1 week's treatment. General improvement began early and continued rapidly. The patient was discharged from the hospital August 27, 1932, free from pellagra symptoms and much improved in weight. We have not been able to follow this patient since her discharge.

With our former cases in this hospital the death rate has varied, but normally, with the dietary form of treatment, we would have expected probably 4 or 5 deaths in a series of 22 cases. In the present series no deaths have occurred. In all probability Cases 6, 10 and 13 of this series would have died if the treatment had been dietary alone.

Strong evidence has recently been developed which seems to prove that a close relationship exists between pellagra and pernicious anemia. Strauss and Castle[10] have shown that the "extrinsic" factor concerned in the production of pernicious anemia is definitely related to vitamin B_2, if not vitamin B_2 itself.

Conclusions. 1. Twenty-two unselected cases of pellagra were treated with liver extract intramuscularly without a death and with rapid marked clinical improvement. We believe that severe cases in either young or old people, which often prove fatal in a short time, can be treated successfully with liver extract.

2. In patients with severe mental depression or marked gastro-

intestinal disturbances who refuse to eat, this method of treatment will give quicker results than dietary treatment.

3. It is simple and much easier to carry out than dietary treatment.

4. A combination of liver extract and the usual dietary treatment would probably give better results than either alone.

5. The time of hospitalization is greatly reduced.

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Note.—Reference 6 is the only reference we have found in the literature on the use of liver extract in the treatment of pellagra. Also we have found nothing which dealt with the parenteral use of liver extract in the prophylaxis or treatment.

In reference 7, Boggs and Padgett stress the value of *liver* in the dietary treatment.

REVIEWS.

PUBLICATIONS OF THE COMMITTEE ON THE COSTS OF MEDICAL CARE. *No. 28, Medical Care for the American People.* The Final Report of The Committee on the Costs of Medical Care, Adopted, October 31, 1932. Pp. 213. Chicago: The University of Chicago Press, 1932. Price, $1.50.

THIS final report of the Committee on the Costs of Medical Care has already been so widely discussed that in a general way its contents are doubtless known to the medical profession—and well they should be, too, as the topic is undoubtedly the most important that will come to this generation of medical men for its decision. And decided it must be, if not by the profession, then by others for them. The time, ability and energy put into amassing and correlating the material for the 28 reports of which this is the summary will hardly ever be equalled for this purpose again; so that whatever our reactions to the conclusions presented, we much recognize our debt to the small group of men who initiated the study and to the foundations that made the study possible.

And how can this report best serve the problem—which can be crudely stated as: how to provide adequate medical at feasible costs. The interpretation of "adequate" is the greatest obstacle in the way of accepting the majority report and the Reviewer agrees with its critics that it is difficult to visualize a highly organized group system of medical care that will preserve the necessary individual relation of physician to patient and avoid the mechanical inefficiency of governmental agencies and the evils of political control on the one hand or the unnecessary exploitation of unscrupulous private combines on the other. No reason is apparent why medicine should take this plunge rather than any other of the basic activities of our national life and certainly the experiences of the various national health insurance schemes in Europe should not lead us to copy them. The minority report, on the other hand, though it recommends the careful trial of new methods, is in effect so unreservedly a bid for a *statu quo* which has proved increasingly impractical that it offers but little constructive guidance to a solution of the problem, especially of its "feasible cost" element. We cannot but regret, then, that the Committee did not content itself with a presentation of facts and, resisting the pressure that of course would be exerted for a statement of recommendations, allow the situation to continue to evolve along the slow and painful lines of trial and error, and the gradual formation of national opinion. The facts presented do not give adequate basis faction and we do not believe that Social Studies have advanced to the point "that Social Evolution may be guided wisely." The times do not yet seem ripe to have any revolutionary change in this fundamental item of civic service forced into operation and the premature effort which this report may precipitate will necessarily produce more heat than energy.

There is one detail about the high cost of medical care that we have not seen emphasized—namely, the unnecessary costly procedures in handling simple cases, which after all constitute well over 90 per cent of the cases seen by physicians. Granted the practitioner's recollection of needed "thorough study of the case" in teaching students, his fear that the half educated family or friends of the patient will otherwise think he is being neglected, the estimate of what the traffic will stand and many similar psychological reasons, nevertheless the evil of unnecessary expense to the patient looms ominously. If the sick of the nation could be given adequate care without frills, we suspect that by this step alone the high cost of medical care would be materially lowered. The half billion dollars wasted annually on quacks and nostrums is another item worth remedying. E. K.

PUBLICATIONS OF THE COMMITTEE ON THE COSTS OF MEDICAL CARE. *No. 22. The Fundamentals of Good Medical Care.* An Outline of the Fundamentals of Good Medical Care and An Estimate of the Service Required to Supply the Medical Needs of the United States. By ROGER I. LEE, M.D., and LEWIS WEBSTER JONES, PH.D., Assisted by BARBARA JONES. Pp. 302; numerous tables. Chicago: The University of Chicago Press, 1933. Price, $2.50.

ALTHOUGH it is far beyond our space limitations to review all the publications of the Committee on Medical Care, we must make an exception for this item on account of its wide sphere of usefulness. Perusal of the first 90 pages by the "intelligent layman" would go far toward reducing prevalent misconceptions about the medical profession, while the remaining section on the medical needs of the people would be equally illuminating to physicians. We agree, too, that "the provision of good medical care is largely a question of organization and costs," a problem to be solved in part at least by conscious redirection of medical activities. "The actual provision of adequate medical care must therefore wait upon a practical solution of the problems of economic organization, in which the questions of cost and the means of payment are paramount. It involves also the solution of difficult problems of technical organization, which will assure not only quantitative sufficiency, but above all the quality of service which can be realized only by the maintenance of the traditionally high standards of the medical professions." E. K.

HOW TO BUDGET HEALTH. Guilds for Doctors and Patients. By EVANS CLARK, Director, Twentieth Century Fund, Inc. Pp. 328; 12 illustrations. New York: Harper & Bros., 1933. Price, $4.00.

THIS work, published by the Twentieth Century Fund, whose President, Edward A. Filene, was one of those most active in the formation of the Costs on Medical Care, may be looked on as a sequel to the publications of that Committee. Focussing on the principles of group practice and group payment recommended in the majority of the Committee's report, this book is a layman's advocacy of a "medical guild plan." A frankly *ex parte* presentation, it suffers from the defects of unbalanced partiality as well as from a lack of appreciation of the basic importance of the individual relation of doctor to patient. As a clear presentation of a definite plan from one side of the doctor-patient combination, it is a useful adjunct to the Committee's literature. E. K.

ACROMEGALY. By F. R. B. ATKINSON, M.D., C.M., EDIN. UNIV. With a Foreword by SIR ARTHUR KEITH. Pp. 260; 3 illustrations. London: John Bale, Sons and Danielsson, Ltd., 1932. Price, 21s.

THE author furnishes a digest of the clinical appearance, pathological anatomy, symptoms and causes, the course of the disease, the various types, pathogeny, diagnosis and treatment of this affection.

The literature has been thoroughly sifted and from 1319 cases elaborate tables present the results of removal of the pituitary gland, the analysis of postmortem examinations, description of the eye conditions, and clinical symptoms and a full bibliography covering 64 pages and 1600 references. While no original work is presented (except for three illustrations of one typical case), the work constitutes a most valuable compend of the subject.

Recognizing that there is no accepted cure for the disease, the author gives a long list of remedies that may afford symptomatic relief. In the field of surgical treatment credit is given to Harvey Cushing and C. H. Frazier, who also find benefit from surgery combined with Roentgen rays. As a possible example of atavism, it is interesting to note that Prof. Keith has revived a view formerly suggested by Freund and H. Campbell bearing on man's descent. The latter considered acromegaly as a reversion to the type of the anthropoid apes and not a true disease. Keith finds the changes in growth in acromegaly are those that occur in anthropoid apes and in the Neanderthal race and attributes them both to hyperpituitarism.

The author refers very briefly to the rôle of acidophile cells which constitute the adenoma of acromegaly and in every case of acromegaly these cells are to be found. The recent suggestion to recognize two hypersecretory states—pituitary acidophilism and pituitary basophilism—is noted but not stressed. The allocation of particular changes in structure and function to particular anterior pituitary cells (chromophobe, acidophile and basophile cells) is important in understanding many of these cases. An index should have been added. G. H.

SPECIAL CYTOLOGY (3 VOLUMES).—By various contributors. Edited by EDMUND V. COWDRY, Washington University, St. Louis. Pp. 1838; illustrated. Second edition. New York: Paul B. Hoeber, Inc., 1932. Price, $30.00.

THIS new edition, expanded into 3 volumes, not only includes much material that has been accumulated in the four years that have elapsed since the first edition; but also in the 9 new sections and 500 more pages makes a fuller presentation of aspects neglected in the first edition. To appreciate the value of such a work, the reader need merely contemplate the labor involved in searching out any notable portion of this information in other standard works or original articles. While the productions of the 46 contributors necessarily vary in excellence, the standard is uniformly high; distinctions may therefore be invidious. Nevertheless, exception should be taken to the out-of-date expression: "little is known concerning the functions of the spleen," while the arteries and veins, the anatomy of the adrenal, cartilage, tendons and fasciæ might be given more space. The abridgement of the section on the pineal with omission of comparative data is also to be regretted. The use of a thinner paper permitting two instead of 3 volumes with a corresponding reduction in cost would have been appreciated by many in these hard times. It is difficult, however, to see how anyone concerned with cytology can continue work without access to this sterling production. E. K.

A HANDBOOK OF EXPERIMENTAL PATHOLOGY. By GEORGE WAGONER, M.D., Associate in Pathology, and R. PHILIP CUSTER, M.D., Associate in Research Pathology, The School of Medicine, University of Pennsylvania. Pp. 160; 22 illustrations, various tables and charts. Springfield, Ill.: Charles C Thomas, 1932. Price, $4.00.

SINCE the time is past for confining the teaching of pathology to morphologic changes, there has been urgent need for a modern book on experimental Mammalian pathology which would bring the subject up to date. Wagoner and Custer do so by directing the student to correlate lesions with functional and chemical changes; thus changes induced in the structure of the

pancreas are correlated with alteration in blood sugar, damage to the liver with changes in the van den Bergh reaction, experimental nephritis with changes in blood nitrogen, and so on.

The first section of the book gives directions for the care of various laboratory animals, with full details for anesthetizing each species. Details of surgical technique essential for the student are included. A most useful feature is a chapter on the normal blood findings in laboratory animals.

The experimental field is considered first from the standpoint of general, then of special pathology. In the former, in addition to the standard experiments on inflammation and the production of various types of lesions, experiments are given on phagocytosis by recently developed techniques, others on the blood sedimentation curve and its modification by experimental procedures. There are also valuable studies in immunity and hypersensitivity.

In the section of special pathology interesting features are the production of reticulocytosis and blockage of the reticulo-endothelium system. Recently acquired knowledge on the endocrine system and vitamins is utilized for students probably for the first time.

The illustrations are clear and forceful. M. McC.

FUNGOUS DISEASES. By HARRY P. JACOBSON, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With Introductions by JAY FRANK SCHAMBERG, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and HOWARD MORROW, M.D., Clinical Professor of Dermatology, University of California. Pp. 317; 153 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $5.50.

THE author does not pretend to cover fungus diseases comprehensively; only the more important clinical ones are included, such as dermatomycosis, moniliasis, maduromycosis, sporotrichosis, blastomycosis, actinomycosis, coccidioidal granuloma, torulosis, and aspergillosis. It is creditable that the author has treated the subject broadly, essaying the more fundamental mycologic phases as well as the clinical ones. He has succeeded in giving a good scientific background on which to superimpose the clinical data.

As might be expected in a first edition, there are many technical errors and some omissions. Some of the typographical errors are annoying because they indicate either carelessness or lack of intimate and first-hand acquaintance with the literature. For example, the name of the foremost medical mycologist, Langeron, is spelled "Langerow" (page 273); Corson and Weigert read "Carson and Weigart" (page 125); on page 273, tokelau reads "tokelaw;" *A. jeanselmei* Ota reads "A. jeanselmeiota," and *A. malignus* Lindt reads "A. Malignus Lindt." On the same page there appear examples of an error extending through the entire book, namely, a failure to italicize the names of specific microörganisms (A. repens, A. flavis, A. herbariorum, A. versicolor). Figures 48 and 84 appear to be upside down.

Illustrations are not consistently good. While many are superlative, others are so meaningless—particularly the photomicrographs—that it would be more creditable to the illustrative phase of the book at large if they were entirely omitted.

It would add to the completeness of the section on coccidioidal granuloma if the Brazilian disease had also received attention, and if its specific agent, *Zymonema braziliensis*, had been distinguished from the agent of the North American disease.

The publishers have done their full part with splendid paper and print. Perhaps the section on laboratory technique (page 63) should be expanded in such a way as to cover sporotrichum, blastomyces, monilia, and so forth, in which case it would deserve a more independent position—perhaps among the fundamental considerations.

These technical errors do not in any way detract from the value of the book as a whole, which has been most useful in bringing together the widely scattered mycologic information on one hand, with the clinical features which have already become much more widely known. The book finds no counterpart in the English language, and if for no other reason merits place in mycologic literature. Jacobson has rendered a distinct service in bringing together a notable accumulation of mycological information.

F. W.

THE PSYCHOLOGIC EFFECT OF MENSTRUATION. By MARY CHADWICK. Pp. 70. New York and Washington: Nervous and Mental Disease Publishing Company, 1932. Price, $2.00.

THE odd and abnormal doings at the menstrual period are here given free Freudian interpretation. Upon primitive woman, it is intimated that the seemingly cruel restrictions imposed, may have been necessitated by her own aberrancy.

N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Asthma, Hay Fever and Related Disorders. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Attending Physician, Cook County Hospital, Chicago. Pp. 124; 8 illustrations. Philadelphia: Lea & Febiger, 1933. Price, $1.50.

A Standard Classified Nomenclature of Disease. Compiled by The National Conference on Nomenclature of Disease. Edited by H. B. LOGIE, M.D., C.M., Executive Secretary. Pp. 701. New York: The Commonwealth Fund, 1933. Price, $3.50.

Irrtümer der Medizin. Neue Gedanken über das Blut- und Nieren-problem. By KURT BERGEL. Pp. 92; 18 illustrations. Leipzig: Bong & Co., 1933. Price, 3 M.

The Committee on the Costs of Medical Care. *No. 22. The Fundamentals of Good Medical Care.* An Outline of the Fundamentals of Good Medical Care and an Estimate of the Service Required to Supply the Medical Needs of the United States. By ROGER I. LEE, M.D., and LEWIS WEBSTER JONES, PH.D., Assisted by BARBARA JONES. Pp. 302; numerous tables. Chicago: The University of Chicago Press, 1933. Price, $2.50. *Abstract No. C 2. The Purchase of Medical Care Through Fixed Periodic Payments.* By PIERCE WILLIAMS. Pp. 18. Washington, D. C.: The Committee on the Costs of Medical Care, 1932. (No price given.)

Nurses. Production, Education, Distribution, and Pay. Report by the Committee on the Grading of Nursing Schools, presenting a few of the outstanding findings from the 2-year study of nursing economics which it carried on in order to secure a fast basis for grading schools of nursing. Pp. 36; 11 illustrations. New York: Committee on the Grading of Nursing Schools, 1930.

How to Budget Health. Guilds for Doctors and Patients. By EVANS CLARK, Director, Twentieth Century Fund, Inc. Pp. 328; 12 illustrations. New York: Harper & Bros., 1933. Price, $4.00. (For Review see page 575 of this Journal.)

Chemical Wave Transmission in Nerve. Based on the Liversidge Lecture Delivered at Cambridge on May 13, 1932. By A. V. HILL, F.R.S., Foulerton Research Professor of the Royal Society; Honorary Fellow of King's College, Cambridge. Pp. 74; 13 illustrations. New York: The Macmillan Company, 1932. Price, $1.25.

Office Surgery. By FENWICK BEEKMAN, Visiting Surgeon, Bellevue Hospital; Visiting Surgeon, Hospital for the Ruptured and Crippled, etc. (Everyday Practice Series, Edited by HARLOW BROOKS, M.D.) Pp. 402; 94 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, $5.00.

Chronic Arthritis and Fibrositis. By BERNARD LANGDON WYATT, M.D., F.A.C.P., Director, The Wyatt Clinic, etc. Pp. 201; 17 illustrations. Baltimore, William Wood & Co., 1933. Price, $3.50.

Food in Health and Disease. By KATHERINE MITCHELL THOMA, B.A., Director of Dietetics, Michael Reese Hospital, Chicago. Pp. 370. Philadelphia: F. A. Davis Company, 1933. Price, $2.75.

Procedures in Tuberculosis Control for the Dispensary, Home and Sanatorium. By BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois; Formerly Medical Director and Member and Secretary, Board of Directors, City of Chicago Municipal Tuberculosis Organization. With a Chapter on Sanatorium Planning by THOMAS KIDNER, New York City, and an Introduction by DAVID J. DAVIS, M.D., PH.D., Dean of the College of Medicine, University of Illinois, Chicago. Pp. 373; 54 illustrations. Philadelphia: F. A. Davis Company, 1933. Price, $4.00.

Case Studies in the Psychopathology of Crime. By BEN KARPMAN, M.D., Psychotherapist, St. Elizabeth's Hospital; Professor of Psychiatry, Howard University, Washington, D. C. Pp. 1026; 14 charts. Washington, D. C.: Mimeoform Press, 1933. Price, $12.00.

The Medical Clinics of North America, Vol. 16, No. 4 (Boston Number—January, 1933). Pp. 256; 33 illustrations. Philadelphia: W. B. Saunders Company, 1933.

The Action of the Living Cell. Experimental Researches in Biology. By FENTON B. TURCK. Pp. 308; 17 illustrations. New York: The Macmillan Company, 1933. Price, $3.50.

Crimes and Criminals. By WILLIAM A. WHITE, A.M., M.D., Sc.D. Pp. 276. New York: Farrar & Rinehart, 1933. Price, $2.50.

Physical Chemistry of Living Tissues and Life Processes. By R. BEUTNER, M.D., PH.D., Professor of Pharmacology, School of Medicine, University of Louisville. Pp. 337; 79 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $5.00.

NEW EDITIONS.

Calcium Metabolism and Calcium Therapy. By ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College, etc. With a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., Late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Pp. 262. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $2.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Effect of Dietary Calcium and Phosphorus on Toxicity of Lead in the Rat: Rationale of Phosphate Therapy.—Several years ago Aub and his associates presented a scientific therapeutic régime in lead poisoning based upon the fact that the metabolism of calcium and lead apparently has a definite parallelism. When there is a negative calcium balance, calcium, and lead if it is present in the body, is deposited in bone. With a positive calcium balance there is an increased elimination of calcium and lead. The solubility of lead phosphate is analogous to calcium phosphate, so that the lead is deposited in the bone in a manner similar to that of calcium. The addition of calcium salt to diets in general results in an increased storage of lime salts in the bone trabeculæ. It was also thought by Aub that the deposition of lead in the bone might be almost instantaneous. This, however, has not been proven and seems to be unlikely. In this new study, in so much as improved calcification of bone following the administration of calcium salts does not take place unless there is adequate phosphorus in the diet, the handling of the patient with lead poisoning has been undertaken on the basis that a certain definite proportion of phosphorus must be included with the calcium. Furthermore, on theoretic grounds alone, it is held that the aim of the treatment of lead poisoning is to deposit or excrete lead in an innocuous form, the phosphate and an abundance of foods containing phosphorus should be given. SHELLING (*Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 248) tested the hypothesis that the introduction of large amounts of calcium without phosphorus merely diverts the available phosphorus to rid the body of excess calcium as a phosphate with consequent interference with the formation of lead phosphate. Thirty-two rats were used, divided into 8 groups of 4 each and were given calcium carbonate, magnesium carbonate, lead carbonate and Na_2HPO_4 in various preparations, together with viosterol. In some instances it was found that the animals receiving vitamin D died sooner than those which did not receive the vitamin, suggesting that the vitamin diverted calcium phosphate into the bones and allowed the lead, uncombined with phosphate, to circulate freely with the body fluids. In the Na_2HPO_4 group, when the phosphate was adequate for both deposition and excretion of both calcium and lead, the animals

did well. Some of the animals were fed the stock diet of lead carbonate until toxic and then were put upon calcium in one group or phosphate in another group. Those receiving the phosphate did well, while calcium-fed animals did poorly. When the phosphate was withdrawn and lead was substituted, the animals did very poorly. The sudden intake of calcium to excess liberated the stored lead causing toxic manifestations. These results indicate that it is essential that a sufficient amount of phosphate be given in the diets of those people suffering from lead poisoning. Aub gives milk, which contains considerable calcium and abundance of phosphorus, but others, not realizing the importance of the phosphorus factor, give large doses of calcium salts other than the phosphate. The phosphate in conjunction with the calcium is important not only in depositing lead in the bones during the acute attacks but also in attempting subsequently the deleading of the individual. This can be done by giving a diet low in calcium and high in phosphorus so that cations taken from the bone are eliminated as insoluble phosphates.

SURGERY

UNDER THE CHARGE OF

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Antiseptics for Skin Sterilization.—During the past 10 years a number of organic mercurial preparations have been offered the profession for use in wound and skin sterilization. In each instance various claims have been made for the superior antiseptic properties of the new substance. In 1925 TINKER and SUTTON (*Ann. Surg.*, 1925, **82**, 640) studied the efficiency and inefficiency of certain skin antiseptics. They found that if the skin was smeared with resistant nonpathogenic bacteria, a soap and water scrub for 2 minutes gave a skin free from bacteria in 30 per cent of cases. Careful ward preparation followed by an ether swab on the operating table gave a skin free from bacteria in 75 per cent of cases, and reduced the colonies in the remainder to a maximum of 3. They found that the selective action of antiseptics was so important that it seemed unwise to depend upon any single antiseptic for skin preparation. Their investigations lead them to the conclusions that iodin preparations and picric acid were too inefficient under ordinary circumstances to be depended upon. Five per cent acriflavin proved to be the most efficient antiseptic which the authors investigated. A 5 per cent solution of mercurochrome in 50 per cent alcohol was approximately as potent as 5 per cent iodin. One year later (*J. Am. Med. Assn.*, 1926, **87**, 1347) the same authors stated that "iodin, trinitrophenol, Harrington's solution, mercurochrome and potassium mercuric iodid will not kill most of the resistant and some of the less resistant, pathogenic bacteria under conditions of perfect contact, and

are still less efficient if penetration is required." They believed that the anilin dyes warranted further investigation and probably wider use. Since these papers the number which have been published on the subject is too lengthy to mention. Many are open to serious question from the standpoint of the technique involved while others have failed to use a sufficiently wide variety of organisms to warrant the claims made in the papers. The frequent sources of error very probably account for the many contradictory notes which have recently been published. The antiseptic properties of the solution may vary with the pH as was shown by HILLER and STAMLER (*J. Urol.*, 1929, **22**, 699), DAVIS (AM. J. MED. SCI., 1921, **161**, 251) and TODD (*Lancet*, 1925, **2**, 1017). BROWNING, COHEN, ELLINGWORTH and GULBRANSEN (*Proc. Roy. Soc. London*, 1930, **105**, 99) and MORGENROTH (*Deutsch med. Wchnschr.*, 1919, **45**, 505) have shown that the presence of serum and proteins may affect the antiseptic properties of the solution. It is interesting that this fact is not considered by most of the pharmaceutical houses in advancing claims for the antiseptics which they are manufacturing. It should be emphasized that culture experiments on different species may be misleading.

BIRKHAUG (*J. Am. Med. Assn.*, 1930, **95**, 917) found the bacteriocidal efficiency of mercurochrome was less than that of hexyl-resorcinol, mercuric chlorid and iodin, but higher than that of phenol. In determining the phenol coefficient of mercurochrome for different organisms the author found these to be as follows: S. aureus, 1.7; S. hemolyticus, 3; B. coli, 2; B. anthracis, 4.6; B. subtilis, 3.7. SIMMONS (*J. Am. Med. Assn.*, 1928, **91**, 704; *J. Infec. Dis.*, 1926, **39**, 273; *Surg., Gynec. and Obst.*, 1933, **56**, 55) found that a 2 per cent solution of mercurochrome failed to kill the S. aureus in 2 minutes or the S. scarlatinæ in 5 minutes. It did, however, kill the S. pyogenes in 2.5 minutes. Simmons found that all mercurochrome solutions which he tried failed to kill the spores of B. anthracis in 3 hours, which was accomplished by tincture of iodin in 1 hour. The papers of TINKER and SUTTON (*J. Am. Med. Assn.*, 1926, **87**, 1347), REDDISH and DRAKE (*J. Am. Med. Assn.*, 1928, **91**, 712), RAIZISS, SEVERAC and MOETSCH (*J. Am. Med. Assn.*, 1920, **94**, 1199), SIMMONS (*J. Am. Med. Assn.*, 1928, **91**, 704; *Surg., Gynec. and Obst.*, 1933, **56**, 55), SCOTT and HILL (*J. Urol.*, 1925, **14**, 135) and SCOTT, HILL and ELLIS (*J. Am. Med. Assn.*, 1929, **92**, 111) report contradictory results on the bacteriostatic and bacteriocidal properties of the various antiseptics used on the skin. A recent report by GERSHENFELD and MILLER (*J. Am. Pharm. Assn.*, 1932, **21**, 894) presents convincing evidence that the bacteriocidal properties of certain of the proprietary organic mercurial preparations are probably in large part due to the acetone and alcohol present in the preparations used for skin sterilization in surgical practice. Although REDDISH and DRAKE (*J. Am. Med. Assn.*, 1928, **91**, 712) reported results from which they concluded that a 2 per cent acetone-alcohol solution of mercurochrome was as efficacious as iodin, the recent studies of SIMMONS (*Surg., Gynec. and Obst.*, 1933, **56**, 55) fail to confirm this, and Simmons infers that Reddish has obtained similar data since his publication. The claims that the new organic mercurial antiseptics penetrate into the deeper tissues of the skin and subcutaneous tissues have not been confirmed by more recent investigations (VON OETTINGEN, *J. Am. Med. Assn.* 1932, **99**, 127;

BISKIND, *Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 37). Tincture of iodin is probably the most commonly used skin antiseptic. Its chief disadvantage is that it frequently irritates the skin. An aqueous iodin solution has been proposed by KARNS (*J. Am. Pharm. Assn.*, 1932, **21**, 779) which is less irritating. BISKIND (*Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 37) found that Karn's solution penetrated the skin more rapidly than did alcoholic solutions of iodin, and GERSHENFELD and MILLER (*J. Am. Pharm. Assn.*, 1932, **21**, 894) found the antiseptic qualities of the two solutions similar. It is evident that we do not as yet have an ideal skin antiseptic. It should always be borne in mind that painting the skin with an antiseptic solution does not render the part bacteriologically sterile. All that one can hope to attain is relative freedom from harmful bacteria. Cleanliness is of primary importance.

THERAPEUTICS

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Renal Diathermy in Renal Hypertension.—Although employment of diathermy in kidney disease goes back a number of years, there is as yet no uniformity of opinion either as to its effects or its therapeutic value. In order to obtain specific data as to its effects RAUSCH (*Deutsch. med. Wchnschr.*, 1932, **58**, 1440) conducted a considerable series of accurately controlled observations upon patients whom he divided into three groups as follows: Group I was made up of those with hypertensive nephrosclerosis in its early stages in which the hypertension was definitely labile; Group II, the same type of patient in the more advanced stage where the hypertension was more or less fixed; Group III comprised patients with chronic nephritis with its secondary hypertension. In the patients in the first group systematic diathermy carried out over periods of several weeks brought about a significant and more or less lasting reduction in blood pressure although this was never brought down to a normal level, the average fall lying between 40 and 60 mm. of mercury. These effects were observed to last for weeks or even months after the cessation of treatment. Striking as they were, the relief of subjective symptoms was even more pronounced in this group of patients. After a few treatments the tendency to vertigo, headache, the sense of pressure within the head, general hyperexcitability and sleeplessness all showed either marked diminution or disappeared practically completely. Similar though far less pronounced effects were produced in the second group. In this group, however, the reduction of blood pressure was insignificant and such benefits as

resulted from the treatment we limited chiefly to some diminution in the subjective symptoms. In the third group no benefit was observed except by way of relief of symptoms especially of the persistent headache. The author discusses the probable mechanisms involved in these effects and points out that they rest chiefly upon an improvement in renal and extrarenal blood flow, both directly and probably indirectly. His technique consisted in placing an electrode of 60 sq. cm. area over each kidney posteriorly and a single lead electrode of 200 sq. cm. over the upper abdomen where it was held by a sandbag. This method of application appeared to place the kidneys most directly within the field of current. The current employed depended upon the patient's sensitiveness to heat and usually lay between 1 to 2 amperes, and the duration of treatment between 45 and 60 minutes. The author feels that the method is of definite help in the treatment of these 3 forms of renal hypertension and that his observations define closely the nature and degree of benefits to be expected.

PEDIATRICS

UNDER THE CHARGE OF

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The Therapeutics of the Intravenous Drip.—HYMAN and HIRSHFELD (*J. Am. Med. Assn.*, 1933, **100**, 305) state that in hemorrhage or dehydration, the intravenous drip will directly restore the fluid volume. In the treatment of shock the drip acts apparently as a corrective for the underlying abnormality in the distribution of the blood. The drip fulfills a twofold purpose in the management of infections. It functions both as a supportive measure and as the ideal route for the administration of specific therapeutic measures. To the surgeon this method possesses value both as a prophylactic against unpleasant postoperative complications and as a therapeutic measure once these untoward events have been established. It may act as a supportive to maintain the patient through a prolonged or shock-producing procedure, and it tends to prevent shock, postoperative thyrotoxicosis, and certain of the common postoperative intestinal disturbances, such as nausea and vomiting, postoperative distention of the stomach, and anuria. By means of the drip the normal level of the blood pressure may be maintained during spinal anesthesia and during exposure of the central nervous system, as during these conditions there may be marked and often alarming fall in blood pressure. The method is of value to the internist in the treatment of toxemias and metabolic abnormalities such as diabetic coma, uremia, cholemia and the intestinal intoxications of infancy and childhood. The dextrose solution also supplies energy, particularly when the enteral routes of administration are not available. There is also some reason to think that the method may be of value in conditions associated with osmotic and colloidal changes in the central nervous system such as occur in poliomyelitis and in encephalitis. In the matter

of the solution used the author's experience was limited to three fluids: physiologic solution of sodium chlorid, dextrose in physiologic solution of sodium chlorid, and blood. They found no occasion for the use of acacia. Dextrose, 5 or 10 per cent, in physiologic salt solution introduced at the rate of 2 or 3 cc. per minute will supply 3000 to 4000 cc. of fluid from 150 to 400 gm. of dextrose yielding from 600 to 1600 calories and adequate salt. Where there is edema or any fear of salt retention, the dextrose may be given in distilled water. If glycosuria occurs, appropriate amounts of insulin may be added directly to the dextrose solution. Other drugs may be administered through the drip such as soluble hypnotics and morphin, epinephrin, digitalis and the like. It also furnishes a convenient avenue for the administration of blood.

The Chemical Action of Sodium Citrate as a Cause of Certain Transfusion Reactions.—Dodd and Bryan (*Am. J. Dis. Child.*, 1933, **45**, 32) point out that dogs with certain chemical abnormalities of the blood are very susceptible to sodium citrate. They show severe and sometimes fatal reactions following the injection of the amounts of citrate ordinarily used as an anticoagulant in blood transfusions. It is probable that children with similar changes in the blood would have the same increased susceptibility to sodium citrate. Although studies on guanidin were not begun when it was first surmised that citrated transfusions were sometimes harmful, poor results have been seen in conditions that the authors now believe to be associated with increased guanidin in the blood. Guanidin is known to have toxic effect other than the production of nervous hyperexcitability and gastrointestinal irritation. Among these are disturbances in carbohydrate metabolism, brought about by interference with the normal metabolism of lactic acid. This condition as well as the nervous symptoms are relieved by calcium. The authors have found that the increase in guanidin level that is associated with severe diarrhea is persistent until normal fluid equilibrium has been reëstablished. Since calcium medication does not decrease the guanidin but merely combats its effects, it seems obvious that any reduction of active calcium by the introduction of citrate might increase the toxic action of the guanidin even in cases in which no marked reaction is precipitated. This may account for the earlier impression that children with gastrointestinal indigestion were sometimes made worse by transfusion of citrate. It seems to make no difference in the reaction whether the sodium citrate reaches the blood stream through gastrointestinal absorption or by direct injection. This suggests that the oral administration of sodium citrate to combat acidosis may be dangerous for children with gastrointestinal indigestion. The ill effects of citrated transfusions of blood in infants with diarrhea may be prevented by the injection of calcium gluconate. As the disadvantages of the citrate method can be so readily overcome by the previous injections of calcium gluconate, the disadvantages are outweighed by the obvious advantages of this method in children. While the intravenous injection of calcium salts is not always free from danger, it has been found that the slow injection of from 3 to 10 cc. of a 10 per cent solution of calcium gluconate is a safe procedure.

Whooping Cough: A Study in Immunization.—SAUER (*J. Am. Med. Assn.*, 1933, **100**, 239) used from 7 to 8 cc. of a relatively fresh pertussis vaccine made from recently isolated, hemolytic strains. These he injected hypodermically in divided weekly doses and seems to have immunized an appreciable number of young susceptible children. During the past 4 years about 300 non-immune children have been injected without any untoward effect. The local reaction is transient. The leukocyte count on the day of the last injection in 60 per cent of the cases ranged from 12,000 to 15,000 per c.mm., with the percentage of small lymphocytes often increased. There have been 8 certain cohabitational or household exposures, and a total of 127 probable or transient or accidental exposures, without any child contracting whooping cough. The 8 cases of definite contact seem to lead to the conclusion that this amount of vaccine will protect, if the interval between injection and exposure is not less than 3 months. Of the 109 children in Group A in 82 instances there were intimate exposure without any child contracting the disease. Among the 94 children of Group B there were 29 such exposures without the development of a case. In Group C consisting of 88 children there were 16 contacts without a case developing. This study is reported at the end of 4 years because the evidence seems sufficiently reassuring to encourage the testing of this method of immunization by others. Use of commercial strains are warned against as long cultivation in the laboratory lead to loss of virulence.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Clinical Observations on Tabetic Arthropathies (Charcot Joints).—KEY (*Am. J. Syphilis*, 1932, **16**, 429) analyzes the records of 69 patients with various expressions of the Charcot arthropathy. He points out that it occurs in from 4 to 10 per cent of tabetics and 25 per cent of cases of syringomyelia. It is distinctly a disease of late adult life, occurs more frequently in males, may involve multiple joints but mostly commonly affects the knee (39 cases), foot and ankle (29 cases), hip (15 cases), spine (5 cases); and joints of the upper extremities rarely (4 cases). In this series of cases only 3 had been precipitated by trauma. The onset may be very acute with apparent resolution of the joint with subsequent recurrence or more commonly the chronic phase supervenes. In all of the cases here reported there was either clinical or serologic evidence of neurosyphilis. One-third of the cases came solely for relief of the joint condition and were unaware of its

constitutional background. The most constant pathologic finding in the entire group was abnormalities of the pupils, only 2 patients having normal pupillary findings. Ninety per cent showed loss of deep reflexes. Among 60 cases subjected to serologic study, the Wassermann was positive in 19 and negative in 41 and in 30 patients with spinal fluid findings, the spinal Wassermann was positive in 11 and negative in 19. While the author advocates aggressive active treatment of the underlying neurosyphilis, he does not believe that treatment will prevent the development of a Charcot joint or stay the progress of a joint already undergoing this type of destruction.

Syphilis and Thyroid Disease With Special Reference to Hyperthyroidism.—NETHERTON (*Am. J. Syph.*, 1932, **16**, 479) gives an exhaustive review of the literature dealing with the association of syphilis and dysfunction of the thyroid gland and analyzes 62 cases from the records of the Cleveland Clinic to ascertain the proper management of such cases. The author cites cases in which syphilis produces a syndrome closely simulating hyperthyroidism, but the basal metabolic rate was within the range of normal. The author concludes that: (1) Antisyphilitic treatment should not replace surgical intervention in cases of active hyperthyroidism in syphilitic individuals, as operation followed by antisyphilitic therapy will prevent the cardiac damage which may result from the unnecessary delay. (2) Syphilis does not interfere with the convalescence of these cases. (3) Pre-operative treatment is advisable but should not be too vigorous. (4) Patients having neurosyphilis associated with hyperthyroidism are poor surgical risks, especially if there is mental deterioration.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Primary Diphtheria of Vulva in Childhood.—Having reviewed the Russian and German literature on the subject, SMORODINZEFF (*Zentralbl. f. Gynäk.*, 1932, **56**, 2118) concludes that primary diphtheria of the vagina and vulva in childhood is a rather unusual disease. After reporting 3 cases of his own he sums up the factors which should aid in making the diagnosis. The most important symptom is painful urination and it is usually the reason for consulting the physician. There is general weakness and nervous restlessness, but the body temperature is normal or only slightly elevated. The external genitalia are markedly edematous, much more so than is seen in gonorrheal vulvovaginitis. The inguinal glands are enlarged and hard. There is a slight, blood-tinged,

mucous discharge in contrast to the profuse purulent discharge seen in gonorrhea. On the vulvar mucous membrane can be found a gray or grayish green membrane which is strongly adherent to the underlying tissues, which bleed when an attempt is made to remove the membrane. In gonorrheal infection the mucous membrane is usually very hyperemic, but in diphtheria there is a characteristic cyanotic appearance and, as a rule, several deep erosions are present. For positive diagnosis, of course, resort must be had to bacteriologic study. The treatment of this condition embraces the usual rules for the treatment of diphtheria. Antitoxin should be given in adequate dosage remembering that intramuscular injection is about six times as efficient as subcutaneous administration, while in very ill cases intravenous injection may be necessary.

Surgical Accidents to Ureter.—Accidents to the ureter during the course of a pelvic operation probably occur with greater frequency than usually reported but, according to BEACH (*J. Urol.*, 1932, **28**, 35), most of them can be forestalled. The risk is greater in vaginal hysterectomy and occurs not so often in ligating the broad ligaments as in seizing obscure "bleeders" at the vaginal vault. The Wertheim operation is particularly treacherous and the originator of this operation is alleged to have had 44 ureteral fistulæ (6 per cent) following his own technique. Precise anatomic knowledge, including morbid deviations and preliminary ureteral catheterization for complicated cases, will prevent disaster. The ureter is most often injured in hysterectomy especially for cancer and frequently for the removal of intraligamentous tumors. The usual sequel is a ureterovaginal fistula. Complete ureteral section disrupts the neuromuscular mechanism of this organ and usually dooms the kidney. The pace of kidney dissolution is determined somewhat by the remedial measure adopted. The best reparative measure is the implanatation of the proximal ureter into the bladder when possible. Even ideal ureteral anastomosis often culminates in segmental atony or stricture with superimposed infection. Nephrectomy should be a last resort, since the other procedures transfer the load gradually to the opposite side, and it should never be done at the time of the accidental injury.

OPHTHALMOLOGY

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Amaurosis in the Preëclamptic State.—According to MAYER (*Zentralbl. f. Gynäk.*, 1931, **55**, 3490), the occurrence of amaurosis as the initial symptom of an eclampsia does not increase the severity of the prognosis for the life of the mother, and conservative treatment can be

employed, if desirable in the interests of the child, if the general condition and renal function of the mother warrant. In a certain percentage of cases the amaurosis is thought to be a functional disturbance without an anatomic basis. No fundus changes are present and the vision soon returns to normal. In other cases, retinitis, hemorrhages or retinal detachments are present. In such cases immediate induction of labor is necessary to save sight. As a rule, amaurosis is only a precursor of true eclampsia, and convulsions will soon follow. In an occasional case, however, under conservative management, vision returns to normal in a few days and the pregnancy continues to term without further complications. Treatment by means of lumbar puncture to reduce the intracranial pressure, and by venesection to lower the blood pressure and for its detoxicating effect, seems to have little influence on the amaurosis. The same holds true for intradural injections of normal pregnant serum. The luminal, Stroganoff, and hunger-diet measures for the control of the convulsions seem not to affect materially the course of the amaurosis. To summarize, latent eclampsia with amaurosis as the initial symptom should be handled in the same way as eclampsia without amaurosis. Conservative treatment is usually of little value from the standpoint of the child because of the frequency of intrauterine death, but, from the standpoint of the life of the mother, carries no greater risk than in eclampsia without amaurosis. For the conservation of the future vision of the mother, delay should be considered only if the fundus is normal.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Vidian Neuralgia.—VAIL (*Ann. Otol., Rhinol. and Laryngol.*, 1932, **41**, 837) says that "vidian neuralgia" is a pain of neuralgic character in the nose, face, eye, head, neck and shoulder, occurring in severe attacks. These cannot be caused by any external stimulation, are not relieved by opiates and are not associated with any subjective loss of sensation. The attacks are most typically unilateral, are often nocturnal and may or may not be associated with subjective symptoms of a nasal sinusitis. After enumerating the various subjective and objective findings of Sluder's sphenopalatine ganglion neuralgia, the author refers to his previously reported case (*Arch. Surg.*, 1929, **18**, 1247) of sphenoiditis which presented "not only the posterior symptoms hitherto assigned to irritation of the vidian nerve, but also the anterior symptoms which Sluder felt were due to irritation of Meckel's ganglion. Believing Sluder to be in error by attempting to differentiate between sphenopalatine ganglion neuralgia and vidian neuralgia, and that the symptoms in the condition under discussion are due to an irritation or inflammation of the vidian nerve and not to any conditions affecting directly the sphenopalatine ganglion, the author quotes anatomic facts to refute Sluder's experiments and "to show that it is impossible to

stimulate the vidian nerve in the sphenomaxillary fossa without involving the sphenopalatine ganglion." Of his 31 personal cases, 28 were in females. He concludes that treatment should be directed towards the disease in the sphenoidal sinus.

Adenoids and Upper Respiratory Disease (Common Cold) in Adults.—Purposing to ascertain any existant relationship between the presence of the pharyngeal tonsil (adenoids) and the frequency, severity and type of attack of the common cold in adults, GAFAFER (*Ann. Otol., Rhinol. and Laryngol.*, 1932, **41**, 517) conducted a series of observations on 252 men and 65 women. Investigations extended over the 35 weeks from October, 1929, to June, 1930. Of the entire group of 317 persons, 235 showed adenoids. As portrayed in the author's tabulations, the presence or absence of adenoids did not seem to make any significant difference in respect of frequency, severity, or type of attack of upper respiratory disease (common cold).

RADIOLOGY

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Roentgenologic Manifestations of Giant-cell Tumor.—In a series of 86 proved cases of giant-cell tumor, 2 roentgenologic types of growth have been encountered with approximately equal frequency by KIRKLIN and MOORE (*Am. J. Roent. and Rad. Therap.*, 1932, **28**, 145). The first variety has been accurately described by many observers. It is a central tumor, situated most often in the end of a long bone, and it exhibits trabeculæ and expands the cortex but does not break through it. Other tumors of bone which may be confounded with this type of giant-cell tumor are enchondromas and cysts of bone. In the second type of giant-cell tumor trabeculation is conspicuously absent. The roentgenograms give evidence of homogeneous lysis of the affected area; the cortex is not only expanded but is dissolved wholly or in part, and the tumor projects into the soft tissues. In many cases the irregularly destroyed cortex has the appearance of a thin layer of melting ice. This variety of giant-cell tumor might be mistaken for primary sarcoma or a massive metastatic growth. Giant-cell tumor is not necessarily confined to the end of a long bone; exceptionally it may occur elsewhere in the shaft. Besides the long bones, the bones of the face, the vertebræ, the ribs and the tarsal bones are subject to the disease. In this series outstanding differences from other series reported were not observed in respect to age and sex of the patients or duration of the disease.

Roentgenologic Evidence of Fetal Death.—From roentgenologic studies of 176 cases of pregnancy including 16 cases in which the fetus was dead, SCHMITKER, HODGES and WHITACRE (*Am. J. Roent. and Rad. Therap.*, 1932, **28**, 349) draw the following conclusions: Roentgenographic demonstration of overlapping of the skull bones of a fetus *in utero* is fairly reliable evidence that the fetus is dead, provided the patient is not in labor and that care has been taken to exclude pseudo-overlapping due to the overlying images of sutures and fontanelles. Absence of overlapping means little. Conclusive evidence is lacking as to the exact relationship between the datum of fetal death and the development of the sign but all agree that some time must elapse. A faint fetal shadow may mask overlapping; hydrocephalus may prevent its development. Spinal angulation and thoracic collapse appear to be of doubtful value as criteria of fetal death. It is dangerous to diagnose decalcification in every instance of a faint or blurred fetal shadow, because early in pregnancy the appearance may be due to a failure to calcify rather than a loss of calcium previously present, and, even in well-calcified skeletons, excessive amniotic fluid, respiratory movement and many technical factors can produce the same appearance. Furthermore, quantitative information is lacking as to the calcium content of the human fetus, either macerated or normal, and some embryologists and clinicians insist that no decalcification occurs in maceration. Anthropometric data published by Scammon and Calkins allow a reasonably accurate opinion as to the age of a fetus if its occipito-frontal diameter is known. Even with very coarse roentgenographic measurements of this diameter, Roentgen estimates of fetal age have agreed surprisingly well with the actual age (as estimated from menstrual or delivery dates) in a considerable number of cases. Disproportion between ages thus calculated and the supposed duration of gestation constitutes a valuable criterion of fetal death and accurate fetometry by stereoroentgenographic methods ought to improve the validity of the diagnosis. Absence of any or all of the criteria does not exclude the possibility that a fetus is dead because they all depend upon the degree of maceration. It seems worth while, therefore, to point out that the roentgenographic diagnosis of movement of a fetal part occurring during the Roentgen examination constitutes conclusive evidence of fetal life.

NEUROLOGY AND PSYCHIATRY

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Psychiatry in the Children's Institution.—MARKEY (*Am. J. Orthopsychiat.*, 1932, **2**, 25) discusses the relationship of the psychiatrist to the children in an orphanage. In the opinion of the assistant superin-

tendent of the institution, a man who has been intensively psychoanalyzed, the psychiatrist may influence the general mental hygiene normally carried on in the institution, but his main service has been to treat directly children whose resistances are great and complex, whose behavior tends to be antisocial and whose personalities appear to be cracking under the strain of life. The psychiatrist's contacts have tended to resolve conflicts, to realign mental powers, to develop for such children a personal ally. The fairly well integrated children are enabled to find better values in life and discontent has been softened; thereby preventing unacceptable reactions. The author believes the psychiatrist has not been as helpful with antisocial as with shut-in children, perhaps because the former pass through all of the administrative levels first. The director of the after-care service believes the psychiatrist has been of great help in the development of wholesome attitudes on the part of the children toward their postgraduate life and its problems, that he has helped her to understand their problems better and to handle them more successfully. She adds that the friendly relationships established by the psychiatrist with children before their graduation makes it a simple matter to continue the contact, through intensive correspondence, even in instances where the children have gone to distant cities. The psychiatrist believes that he has become an integral part of the medical and social organization of the institution, but finds that his functions are limited because they overlap and might tend to repeat the professional angle of the administrative function. This, therefore, makes him less important and a less absolute support than the physician is in his field. He has, in psychiatric fashion, also avoided the use of absolute insistence on carrying out his recommendations and has tended right along to avoid encroaching on the administrative prerogative of decision. This has tended further to make him positive than the physician. An objective atmosphere has developed with a resultant lessening of dramatic reactions to acute problems and a probable decrease in the incidence of major problems. Treatment is now almost automatically based on cause; taboos and repressions play a minor part in discipline, and methods are now seen to be more valuable than results.

PATHOLOGY AND BACTERIOLOGY

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The Systemic Effects of Histamin in Man.—An investigation upon the effects of histamin administered intravenously in the human subject has been recently carried out by WEISS, ROBB and ELLIS (*Arch. Int. Med.*, 1932, **49**, 360). An average dose (0.001 mg.) was found to

produce flushing, an increase in the heart rate, electrocardiographic changes and a slight fall or rise in blood pressure. An increase in the pressure of the cerebrospinal fluid with a dilatation of the small cerebral vessels was also observed. The above changes occurred very rapidly and disappeared 2 or 3 minutes after the injection. Continuous intravenous administration of histamin in general produced similar effects, which lasted as long as the drug was given. Cardiovascular response depended upon the rate rather than the duration of the injection, the cardial output being increased and the blood pressure remaining essentially unaltered. An elevation of the basal metabolic rate and a slight rise in the hemoglobin combining power were also noted. The respiratory mechanism was not appreciably affected. No subjective or objective changes were observed following the oral administration of histamin, even in massive doses. Attention is drawn to the similar effects of this drug and physical exercise. The absence of a fall in blood pressure and the failure of even toxic doses to produce symptoms of shock in the human subject would tend to discredit the rôle ascribed to histamin in the production of this condition.

Experimental Thromboangiitis Obliterans.—Horton and Dorsey (*Arch. Path.*, 1932, **6**, 910) in a series of experiments carried on over a period of $2\frac{1}{2}$ years, report that they were able in many instances to produce vascular lesions in rabbits, similar to if not identical with the human lesion in thromboangiitis obliterans. This was accomplished by bacterial injection, or implantation of tissue known to be infested by similar organisms. The bacteria were cultured from 56 patients with thromboangiitis obliterans, and 10 patients with arteriosclerotic disease of the lower extremities. The organism most commonly present was a pleomorphic streptococcus. In addition green streptococci, staphylococci and Gram-negative bacilli were found. In a word, the authors were able to produce, in a fair number of instances, the described lesions with endothelial proliferation and thrombosis, by injection of pleomorphic streptococci, either intravenously or intramuscularly. The streptococci were those found in pure culture in bloodvessels of patients known to have thromboangiitis obliterans. Portions of vessels from patients with thromboangiitis obliterans were imbedded adjacent to femoral vessels with 24.1 per cent positive results. Results were 23.8 per cent positive in intramuscular injection, and 15.3 per cent positive in intravenous injection. Injection of organisms obtained from extracted teeth, tonsils and other foci of infection in thromboangiitis patients gave entirely negative results. The authors state that as far as they know, these are the first lesions of this type that have been produced in experimental animals and suggest that the disease is of infectious origin, possibly with the streptococcus as the etiologic agent.

The Induced Development of Nonacid-fast Forms of Bacillus Tuberculosis and Other Mycobacteria.—Since Koch, bacteriologists have been aware of the existence of nonacid-fast forms of the tubercle bacilli. Their place in the life cycle of the mycobacteria has not been generally accepted, since it has always been difficult to rule out contamination. Miller (*J. Exp. Med.*, 1932, **56**, 411) has been able, by adding a sterile extract of his "chromogenic H-37 strain of human tubercle

bacilli" to media on which certain acid-fast forms were growing, to wean these over to nonacid-fast forms. The strains were Saranac H-37, T. S., and 90, a bovine strain B-1, a smegma strain 74, and a Saranac strain of Bacillus phlei. Ten-day growths of the above mentioned strains were used in the experiments. One to 10 cc. of filtered extract was added to a fresh transplant of each of these growths. In some cases, second and third additions of extract were made before microscopic or macroscopic changes were noted. Transplants were made in 5 days, 2 weeks, 4 weeks, and 6 weeks. The organisms were finally grown on agar, and in many cases, smears of such growth were entirely nonacid-fast. In 4 of the strains, return to acid-fastness was induced by growth on Petroff's egg media. Peculiar morphologic changes are described. Control plates of the extract were always sterile. The fact that similar results were obtained in experiments carried on simultaneously in New York and Cleveland lessens the probability that contamination was responsible for the results obtained.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Public Health Aspects of Frozen Foods.—FELLERS (*Am. J. Pub. Health*, 1932, **22**, 601) states that frozen food factories are clean and modern methods of sanitation are used in preparing the many perishables now packed. The quality of the raw product is high, and if the freezing is prompt and rapid and the storage kept at low, constant temperatures, little or no deterioration in quality, appearance or nutritive value occurs. Several types of very efficient mechanical equipment are available to carry out the freezing process. Fish, meats, poultry, eggs and oysters are especially well preserved by freezing because they retain more nearly their fresh appearance, flavor and character than fruits or vegetables. Most fruits are best when frozen with sugar and in this form retain their flavor very well. Vegetables are the most recent addition to the list of frozen foods. Though some varieties freeze very well, others do not. Both fruits and vegetables bleed freely on thrawing. Spoilage occurs very quickly in vegetables after defrosting. More research is urgently required on the microbiology of frozen flesh foods and vegetables. Little change occurs in the chemical, enzymic or nutritive properties as a result of freezing. The changes are largely physical. Freezing greatly reduces the number of microörganisms present in foods and prevents their multiplication. Emphasis must be placed on the prompt utilization of frozen foods. Until more is known

about the subject, frozen products should be consumed while still frozen or within a very few hours after defrosting. The ready availability of a large variety of frozen foods at all seasons will serve to give variety to the human diet and should aid in decreasing nutritional deficiency diseases.

The Metamorphoses of Streptococci into Spore-bearing Rods and into Filtrable Forms.—EVANS (*U. S. Pub. Health Rep.*, 1932, **47**, 1723) claim that a streptococcus, a filtrable form, and an aërobic spore-bearing rod are phases in the life cycle of an organism cultivated from cases of epidemic encephalitis and from the so-called herpetic and encephalitic viruses. The details of the transition from one form to the other are described in a few instances which exemplify metamorphoses that have been observed many times. The observations described in the present paper are discordant with the monomorphic theory, now discarded by most bacteriologists, but they are in agreement with the laws of general biology. As pointed out by the writer in an earlier paper (1929), from the point of view of general biology, complex life cycles with metamorphoses accompanied by changes in habitat and biologic behavior should be expected in bacteria, rather than monomorphism. Life cycles are a law of Nature; and with the descent in the scale of life, the cycles become more and more complex, and metamorphoses, with the concomitant changes in habitat and in biologic behavior, become more and more pronounced. Algæ, fungi and protozoa—the plant and animal groups stand next higher than the bacteria—exhibit marvelous life cycles. It is unreasonable to think that a law of Nature which becomes more and more complex with the descent in the scale of life would be suspended in its lowest known form.

Primitive or Filtrable Forms of Bacteria and Their Occurrence in Aseptic Milk.—BRUECKNER and SHERMAN (*J. Infec. Dis.*, 1932, **51**, 1) have demonstrated that primitive forms of bacteria were present in the aseptically drawn milk of a majority of the healthy cows studied. The method used for the detection and quantitative estimation of these types of microörganisms was to make serial dilutions of the milk in dextrose beef infusion broth and to incubate the dilution cultures for 1 day at 37° C., and then at 30° C. for about 2 weeks. After incubation the broth cultures from the higher dilutions, which showed no growth of ordinary bacteria, were seeded on the surface of dextrose beef infusion agar. After incubation at 37° C. for 2 days the plates were examined microscopically for the presence of definite, minute colonies. Positive growths were verified by the finding of definite bacterial cells in stained preparations. The results reported in the present paper, as well as other work in the same laboratory, indicate that the primitive forms of bacteria may sometimes occur in numbers approximating a trillion (10^{12}) per gram of substance. The morphologic types observed were cocci and small rods. While the life cycle theory of previous investigators is a plausible and attractive explanation of the results obtained, the work reported here does not answer the question of whether these organisms are definite species or represent only a dissociative form or cyclo-stage in the development of ordinary bacteria.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1933.

Criticism of Weighing by Single Deflections.—SAMUEL E. POND (Laboratory of Physiology, University of Pennsylvania). Analytical balances adapted for weighing by single deflections[1] have been critically examined for reproducibility of turning point over several months. One balance[2] has been employed regularly for rapid weighing of fresh tissues, routine quantitative analysis and for precision calibrations of weights in comparison with calibrations by other methods on more sensitive balances. Not only has time been saved but good accuracy has been maintained. Care had to be taken, however, to avoid changes observed in the reference point of the unloaded balance.

A source of varying error has been overcome by coördination of the beam lifting mechanism with the pan-arresting device, such as to prevent lateral displacement of the pointer. It was necessary in order to insure accuracy that the pointer-tip be adjusted to the top of one particular scale line, and this juxtaposition read with minimum of parallax, by means of lens and sight. Estimates were not made of distance, but alway when coincidence was established. The major adjustment required that the right-pan stop be slightly clear from the pan at rest, at mean temperature. When and after this was done a high order of reproducibility of results was secured with temperature changes not exceeding 2° C. per hour outside the balance case. The same sensibility, at 7 seconds per half period, *i. e.*, ± 0.05 mg., with 100 gm. in each pan, has been maintained for several weeks. The reference point has varied less than 0.1 scale division from day to day. Calibrations of weights to 1×10^{-4} gm. have been completed in about 3 hours combining the method of substitution, *i. e.*, Borda's technique with single deflections, against 20 hours other things equal except that the method of oscillations was substituted. Similar materials, consisting of crucibles, have been conveniently weighed to $\pm 5 \times 10^{-5}$ gm., about 30 per hour, as against 8 per hour, comparing single deflections, checked three times, against −3:2 oscillations checked similarly.

Metabolism of Galactose in Diabetes Mellitus.—W. G. KARR, and T. V. LETONOFF (Laboratories of the Division of Metabolic Diseases, Philadelphia General Hospital). Much confusion has existed with regard to the metabolism of galactose. When it is given by mouth many investigators have found it disappearing from the blood very rapidly.

[1] Turner, R. R.: "Chemist-analyst," No. 16, 1916, p. 21; Brinton, H. M. P.: J. A. C. S., 1919, vol. 41, p. 1151.

[2] Troemner: No. 16.

Others have found a marked rise in total sugar and have formed the general conclusion that galactose is a poor glycogen former.

Tolerance studies in animals have more uniformly shown a decreased utilization. Cori and Cori[1] have also concluded, on the basis of feeding galactose to rats and analyzing their livers, that galactose does not form glycogen as readily as do glucose and fructose. Row and Schwartzman[2] repeated previous experiments done on normals and also did tolerance studies on diabetics. They concluded that galactose disappears from the blood as readily in diabetes as in normal individuals, and suggested that galactose might be more available to the diabetic than other carbohydrates.

Their experiments only included a 2-hour blood and urine study. It was thought that a study of galactose utilization in a diabetic over a longer period of time might throw additional light on its metabolism. A diabetic of long standing on the ward was chosen for the experiment. He was well controlled with insulin and diet, and at the time of experiment was on a diet of protein, 60; fat, 190; carbohydrate, 60; with 18 units of insulin in the morning and 12 at night.

For certain experiments insulin was withheld for 24 hours, and a study made of glucose and galactose tolerances. For the long time experiments 100 gm. of additional carbohydrate was given with his diet and insulin, divided in equal portions over the three meals. The increased glycosuria and glycemia were studied with the addition of galactose for one period, glucose and starch for similar comparative periods.

The comparative tolerance studies upon the patient without insulin for 24 hours showed the following results:

Galactose disappeared from the blood in 3 hours, and a certain portion was found in the urine. True glucose in the blood increased with the galactose feeding. The hyperglycemia from feeding equivalent amounts of glucose was much greater than the total sugar after galactose feeding. Sugars taken at 3.00 P.M., after a regular lunch, were of the same elevation, no matter what the carbohydrate fed, and continued so for the remainder of the day, and give similar fasting blood sugars the next morning. Respiratory quotient studies taken over this period showed that galactose was not burned in the body in any greater quantities than other ingested carbohydrates. There was a glycosuria after galactose feeding, but the glycosuria after glucose feeding was much greater.

On another day 50 gm. of galactose was given the patient with 18 units of insulin 15 minutes before the galactose feeding. The disappearance of the galactose from the blood stream with the previous dose of insulin was no greater than when insulin was not given. Insulin is not concerned with the removal of galactose from the blood.

Comparison of the long time experiments of feeding the carbohydrate three times a day, as indicated above, gave the following results:

On the galactose period the average urine glucose was 3.06 gm. daily. The average galactose excretion was 4.57 gm. During the glucose period the average daily glucose excretion was 9.42 gm. During the starch period the average daily glucose excretion was 7.01 gm. The average

[1] Cori, C. F., and Cori, G. T.: J. Biol. Chem., 1926, **70**, 557.
[2] Roe and Schwartzman: J. Biol. Chem., 1932, **96**, 717.

of 18 fasting blood sugars during the galactose period was 155 mg. per 100 cc.; during the glucose period 157 mg.; during the starch period 162 mg. The average of 11 fasting blood sugars on insulin and diet alone was 124 mg.

We may conclude from these experiments that the state of the diabetes, as measured by the fasting blood sugar, was the same in all three periods.

Glycosuria was slightly greater during the glucose period, as would be indicated by the previous tolerance experiments.

The following general conclusions may be drawn:

1. Galactose disappears very quickly from the blood in a patient with diabetes mellitus.

2. It is not burned, a small portion is excreted, probably little is changed directly to glucose, and it disappears so completely that it seems improbable that there is tissue storage. We are, therefore, able to suggest that galactose forms glycogen very readily in the diabetic.

3. Insulin does not aid in the removal of galactose from the blood stream.

4. Feeding of galactose for a period of a month does not suggest that it is valuable in diabetes, with the exception that the immediate glycosuria and hypoglycemia, after a meal, is somewhat decreased.

NOTE.—We are indebted to Smith, Kline and French, Philadelphia, for supplying the galactose without charge.

The Kinetics of CO_2 Reactions in Buffer Systems.—WILLIAM C. STADIE and HELEN O'BRIEN (From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia). The velocity of the reactions of all forms of CO_2 with the constituents of a buffer system are dependent upon the slow reactions

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \qquad (1)$$

$$CO_2 + OH^- \rightleftarrows HCO_3^- \qquad (2)$$

Toward the right, these equations express the *hydration* of CO_2, toward the left, the *dehydration* of carbonic acid. The velocity of the reaction (hydration or dehydration) is given by the equation

$$-\frac{d\,a_{CO_2}}{dt} = k_1 a_{CO_2}\, a_{H_2O} - k_2 a_{H_2CO_3} + k_3 a_{CO_2}\, a_{OH^-} - k_4 a_{HCO_3^-} \qquad (3)$$

Two general cases arise.

I. The reactions occur in infinite buffer, *i.e.*, the pH is constant. Equation 3 may then be integrated and gives two equations (1) for hydration and (2) for dehydration which permit the calculation of the time necessary to reach any degree of equilibrium, *e.g.*, 90 per cent from the experimentally determined values of the constants k_1, k_2, k_3, and k_4.

II. The reactions occur in dilute buffer, *i.e.*, the pH is variable. Three cases arise.

1. The pH is < 8.5. Reaction 2 becomes negligible.

(*a*) The hydration of CO_2. The velocity is given by the equation

$$-\frac{d\,a_{CO_2}}{dt} = \frac{d\,a_{HCO_3^-}}{dt} = k_1 a_{CO_2}\, a_{H_2O} - k_2 a_{H_2CO_3} \qquad (4)$$

This equation may then be integrated and the velocity constant k_1 determined experimentally from the changing values of $a_{HCO_3^-}$ against time.

(*b*) The dehydration of CO_2. The velocity is given by the equation

$$\frac{d\, a_{H_2CO_3}}{dt} = k_2 a_{H_2CO_3} - k_1 a_{CO_2} a_{H_2O} \qquad (5)$$

This equation may then be integrated and value of k_2 determined experimentally from the changing values of $a_{H_2CO_3}$ against time.

2. The pH is > 12. Reaction 2 then becomes negligible.

(*a*) Hydration of CO_2. The velocity is given by the equation

$$-\frac{d\, a_{CO_2}}{dt} = k_3\, a_{CO_2} a_{OH} - k_4 a_{HCO_3^-} \qquad (6)$$

which may be integrated and the value of the constant k_3 determined experimentally.

(*b*) Dehydration of CO_2. At pH > 12 this is insignificant. For this reason the term $k_4 a_{HCO_3}$ may be neglected in equation 6.

3. The pH is > 7.5 < 12. The complete equation 3 must be used. An integral exists but is too cumbersome for practical use.

The Simultaneous Measurement of Cell Permeability to Water and to Dissolved Substances.—M. H. Jacobs (Laboratory of Physiology, University of Pennsylvania). In order that accurate comparisons may be made between the permeability of different cells to the same substance, of the same cell to different substances, and of the same cell to the same substance at different times, it is desirable to define permeability by an appropriate physical constant which has a real quantitive significance under all these conditions. During the past few years "permeability constants" have been fairly extensively employed by several workers in studying the rate of penetration of cells by water. Corresponding constants for dissolved substances, however, being more difficult to obtain, have as yet been little used. The present method permits not only the accurate determination of permeability constants for dissolved substances but at the same time those for water as well. The principle of the method consists in placing a cell in an originally isotonic solution (*e. g.*, sea water in the case of the egg of Arbacia) to which a penetrating substance has been added in known amount, and in then measuring the volume changes which occur during the shrinkage of the cell and the subsequent recovery of its original volume. Knowing the initial and the minimum cell volumes and the time required to reach the latter, the values of the two permeability constants in question may immediately be read off from a chart prepared by solving by a numerical method the differential equations which describe the penetration of the solute and of water respectively. The application of this method to published data of Stewart and Jacobs indicates that on fertilization the permeability of the egg of Arbacia to ethylene glycol and to water are increased to approximately the same extent. It also indicates that the effect of temperature on the permeability of the unfertilized egg to ethylene glycol is greater than the corresponding effect in the case of water. It is planned to extend the method to a variety of other problems in the field of cell permeability.

Studies on Contraction of Arterioles.—E. R. Clark, E. L. Clark and E. A. Swenson (Laboratory of Anatomy, University of Pennsylvania). In the various types of transparent chambers permanently

installed in the rabbit's ear it has been possible to study the finest cytologic details of bloodvessels and other tissues and the circulatory changes simultaneously in the living mammal. As we described previously (Clark and Clark, *Am. J. Anat.*, 1932, **49**, 441) spontaneous rhythmic contractions of arteries and arterioles and of localized parts of such vessels occur normally from 1 to 4 times a minute in the rabbit's ear. Motion pictures have been taken which show these spontaneous contractions, as well as those which occur after stimulation of the animal, in arteries and arterioles of both the original tissue of the ear and of the newly grown (regenerated) vessels. It has been possible to take pictures in which the outlines of the walls and, in many cases, the microscopic details of the walls (endothelial nuclei, adventitial cells and muscle cells) can be clearly seen.

In motion pictures of the original vessels of the ear with their nerve supply intact it has been possible to obtain accurate measurements of the diameters of arterioles and of arteriovenous anastomoses of various sizes, and to show the time consumed in their contractions. Arteriovenous anastomoses with inside diameters of 0.015 to 0.020 mm. contract in approximately $\frac{1}{2}$ second, while the contraction of arterioles from 0.020 to 0.4 mm. inside diameter, consumes an amount of time varying from $1\frac{1}{2}$ seconds in the smaller to 6 seconds in the larger.

The pictures also add to evidence previously presented that the control of the peripheral circulation in the rabbit's ear resides in the arterioles, while the capillaries and venules are passive.

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